Tofersen (Qalsody™)

Biogen GmbH

Anhang 4-G zu Modul 4 A

Tofersen ist angezeigt zur Behandlung von Erwachsenen mit amyotropher Lateralsklerose (ALS), die mit einer Mutation im Superoxid-Dismutase 1 (SOD1)-Gen assoziiert ist

Im folgenden Dokument wurden bestimmte Teile des Textes und der Tabellen geschwärzt, um die Verblindung der noch laufenden VALOR Open Label Extension (OLE)-Studie aufrechterhalten zu können bzw. eine Entblindung zu verhindern. Die Schwärzungen im Dossier sind analog zu den Schwärzungen in den eingereichten Dokumente im Rahmen des EMA-Zulassungsverfahrens erfolgt.

Stand: 01.07.2024

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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
Age categories (years)	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
18-<35	2 (9.5)	7 (17.9)	[redacted]		2 (5.6)	10 (13.9)	12 (11.1)
35-<50	6 (28.6)	17 (43.6)			15 (41.7)	32 (44.4)	47 (43.5)
50-<65	9 (42.9)	8 (20.5)			14 (38.9)	21 (29.2)	35 (32.4)
>=65	4 (19.0)	7 (17.9)			5 (13.9)	9 (12.5)	14 (13.0)
Age (years)							
n	21	39	15	33	36	72	108
Mean (SD)	54.0 (12.16)	47.3 (14.30)	47.3 (9.79)	49.0 (10.49)	51.2 (11.57)	48.1 (12.64)	49.1 (12.33)
Median	55.0	45.0	49.0	48.0	51.5	47.5	48.0
Q1, Q3	46.0, 61.0	37.0, 58.0	36.0, 53.0	42.0, 57.0	44.5, 58.5	39.0, 57.0	39.5, 58.0
Min, Max	28, 73	23, 78	35, 69	23, 68	28, 73	23, 78	23, 78
Sex	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Male	11 (52.4)	22 (56.4)	8 (53.3)	21 (63.6)	19 (52.8)	43 (59.7)	62 (57.4)
Female	10 (47.6)	17 (43.6)	7 (46.7)	12 (36.4)	17 (47.2)	29 (40.3)	46 (42.6)
Ethnicity	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Hispanic or Latino	[redacted]		1 (6.7)	2 (6.1)	1 (2.8)	4 (5.6)	5 (4.6)
Not Hispanic or Latino			11 (73.3)	20 (60.6)	28 (77.8)	47 (65.3)	75 (69.4)
Not reported			3 (20.0)	11 (33.3)	7 (19.4)	21 (29.2)	28 (25.9)
Race	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
American Indian or Alaska Native	0	0	[redacted]		[redacted]		0
Asian	1 (4.8)	1 (2.6)					9 (8.3)
Black or African American	0	0					1 (0.9)
Native Hawaiian or Other Pacific Islander	0	0					0
White	16 (76.2)	28 (71.8)					69 (63.9)
Not reported	4 (19.0)	10 (25.6)					28 (25.9)
Other	0	0					1 (0.9)

Source: biib067/233as101-partc/csr/t-demog.sas **Run Date:** 22SEP2021

233AS101 Part C: Demography - by population

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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
Height (cm)							
n	21	39	15	33	36	72	108
Mean (SD)	170.9 (10.69)	170.8 (10.20)	169.1 (10.60)	172.6 (9.09)	170.2 (10.54)	171.6 (9.68)	171.1 (9.95)
Median	171.0	170.0	170.0	171.0	170.5	171.0	171.0
Q1, Q3	165.0, 177.0	164.0, 178.0	160.0, 177.0	166.0, 180.0	162.5, 177.0	165.0, 180.0	164.5, 178.0
Min, Max	146, 192	151, 189	151, 188	150, 187	146, 192	150, 189	146, 192
Weight (kg)							
n	21	39	15	33	36	72	108
Mean (SD)	81.87 (19.391)	77.70 (19.424)	77.43 (26.886)	78.18 (16.240)	80.02 (22.560)	77.92 (17.912)	78.62 (19.503)
Median	81.90	74.60	72.80	78.10	78.55	75.60	76.75
Q1, Q3	74.60, 92.70	63.00, 87.00	58.50, 85.00	68.30, 85.00	65.15, 92.70	65.10, 85.80	65.15, 88.30
Min, Max	45.0, 113.4	49.4, 146.5	42.5, 136.3	44.8, 115.0	42.5, 136.3	44.8, 146.5	42.5, 146.5
BMI (kg/m^2)							
n	21	39	15	33	36	72	108
Mean (SD)	27.98 (6.187)	26.65 (6.404)	26.61 (7.035)	26.15 (4.633)	27.41 (6.491)	26.42 (5.629)	26.75 (5.919)
Median	27.38	25.63	24.69	24.79	25.68	25.21	25.37
Q1, Q3	24.35, 31.11	22.09, 28.66	22.03, 29.41	23.84, 27.74	23.41, 30.60	22.66, 28.18	23.09, 29.10
Min, Max	15.8, 38.0	18.6, 45.2	16.4, 44.5	17.9, 38.0	15.8, 44.5	17.9, 45.2	15.8, 45.2

Source: biib067/233as101-partc/csr/t-demog.sas **Run Date:** 22SEP2021

233AS101 Part C: ALS disease history - by population

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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
Confirmed SOD1 mutation	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Yes	21 (100.0)	39 (100.0)	15 (100.0)	33 (100.0)	36 (100.0)	72 (100.0)	108 (100.0)
No	0	0	0	0	0	0	0
Protocol defined SOD1 mutation	21 (100)	39 (100)	NA	NA	36 (100)	72 (100)	108 (100)
Yes	8 (38.1)	17 (43.6)	NA	NA	8 (22.2)	17 (23.6)	25 (23.1)
No	13 (61.9)	22 (56.4)	NA	NA	28 (77.8)	55 (76.4)	83 (76.9)
Mutation type	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Intronic	[redacted]						
p.Ala141Gly							
p.Ala146Thr							
p.Ala5Ser							
p.Ala5Thr							
p.Ala5Val							
p.Ala90Thr							

NOTE 1: Protocol defined mutation includes p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly.
NOTE 2: Time since ALS symptom onset is calculated in months as (date of baseline ALSFRS-R score - date of ALS symptom onset)/30.4375.
NOTE 3: Subjects who have more than one site of onset are summarized under 'Multiple sites'.
NOTE 4: Time since ALS diagnosis is calculated in months as (date of baseline ALSFRS-R score - date of ALS diagnosis)/30.4375.
NOTE 5: Pre-randomization ALSFRS slope is calculated using the (ALSFRS-R score at baseline (Day 1) - maximum possible score of 48)/duration of symptom onset, where duration of symptom onset is calculated as (date of baseline ALSFRS-R score - date of symptom onset)/30.4375.
NOTE 6: Partial date with missing day is imputed with 15th of the month and partial date with missing month/day is imputed with January 15th for the calculations.
NOTE 7: King's staging is based on clinical milestones that consider involvement of 1-3 anatomical regions of bulbar region, upper limbs and lower limbs (Stage 1 = 1 region, Stage 2 = 2 regions, Stage 3 = 3 regions), the need for gastrostomy (Stage 4a), non-invasive ventilations (Stage 4b) and death (Stage 5); the higher stage takes precedence and is assigned to the subject.
(a) Numbers in parentheses are percentages and calculated based on the number of subjects in each treatment group.
Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; SOD1 = superoxide dismutase 1.
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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
p.Ala90Val	[redacted]						
p.Arg116Gly							
p.Asn87Ser							
p.Asp102Gly							
p.Asp125Val							
p.Asp91Ala							
p.Gln23Leu							
p.Glu101Gly							
p.Glu101Lys							
p.Glu50Lys							
p.Gly13Arg							
p.Gly148Ser							
p.Gly38Arg							
p.Gly42Asp							
p.Gly42Ser							
p.Gly94Ala							

NOTE 1: Protocol defined mutation includes p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly.
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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
p.Gly94Arg	[redacted]						
p.Gly94Asp							
p.Gly94Cys							
p.Gly94Ser							
p.His121Gln							
p.His44Arg							
p.His47Arg							
p.Ile113Thr							
p.Ile114Thr							
p.Ile150Thr							
p.Leu127Ser							
p.Leu145Phe							
p.Leu145Ser							
p.Leu39Val							
p.Leu85Phe							
p.Phe21Ile							

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p.Phe65Leu p.Thr138Ile p.Val149Gly	[redacted]						
Time since ALS symptom onset (months)							
n	21	39	15	33	36	72	108
Mean (SD)	9.23 (5.791)	8.41 (3.658)	45.35 (26.332)	44.84 (35.663)	24.28 (24.953)	25.11 (30.241)	24.83 (28.472)
Median	8.28	8.25	39.56	35.48	14.59	11.37	11.79
Q1, Q3	5.06, 12.09	5.98, 10.38	30.29, 53.62	19.45, 60.88	6.55, 31.95	7.21, 28.85	7.21, 31.72
Min, Max	2.4, 21.3	1.7, 18.5	11.8, 103.2	3.9, 145.7	2.4, 103.2	1.7, 145.7	1.7, 145.7

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Site of onset	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Bulbar	[redacted]		[redacted]		[redacted]		6 (5.6)
Lower limbs							72 (66.7)
Upper limbs							27 (25.0)
Respiratory			0	0			1 (0.9)
Thoracic			0	0			0
Multiple sites			0	0			2 (1.9)
Time since ALS diagnosis (months)							
n	21	39	15	33	36	72	108
Mean (SD)	4.32 (3.956)	3.08 (2.625)	17.80 (18.095)	20.49 (21.842)	9.94 (13.614)	11.06 (17.176)	10.69 (16.021)
Median	3.61	2.27	13.77	15.74	5.45	4.07	4.70
Q1, Q3	1.05, 5.65	1.12, 4.21	5.39, 32.20	5.06, 25.36	1.89, 11.25	1.82, 12.94	1.82, 12.94
Min, Max	0.2, 16.8	0.5, 12.5	0.9, 66.8	1.3, 101.8	0.2, 66.8	0.5, 101.8	0.2, 101.8

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Pre-randomization ALSFRS-R slope							
n	21	39	15	33	36	72	108
Mean (SD)	-1.809 (1.1715)	-1.735 (1.5765)	-0.260 (0.2541)	-0.303 (0.1969)	-1.164 (1.1875)	-1.079 (1.3654)	-1.107 (1.3038)
Median	-1.512	-1.338	-0.165	-0.303	-0.892	-0.747	-0.767
Q1, Q3	-2.124, -0.958	-1.734, -0.965	-0.528, -0.075	-0.366, -0.166	-1.765, -0.187	-1.365, -0.310	-1.424, -0.286
Min, Max	-4.91, -0.42	-8.30, -0.39	-0.84, -0.02	-0.77, 0.00	-4.91, -0.02	-8.30, 0.00	-8.30, 0.00
Disease progression subgroup	NA	NA	NA	NA	36 (100)	72 (100)	108 (100)
Enriched	NA	NA	NA	NA	21 (58.3)	39 (54.2)	60 (55.6)
Other	NA	NA	NA	NA	15 (41.7)	33 (45.8)	48 (44.4)
Riluzole use	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Yes	13 (61.9)	25 (64.1)	9 (60.0)	20 (60.6)	22 (61.1)	45 (62.5)	67 (62.0)
No	8 (38.1)	14 (35.9)	6 (40.0)	13 (39.4)	14 (38.9)	27 (37.5)	41 (38.0)

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	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
Duration of riluzole use (days)	[redacted]		9 (100)	20 (100)	22 (100)	45 (100)	67 (100)
< 30			1 (11.1)	1 (5.0)	1 (4.5)	2 (4.4)	3 (4.5)
>= 30			8 (88.9)	19 (95.0)	21 (95.5)	43 (95.6)	64 (95.5)
Edaravone use			15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Yes			2 (13.3)	4 (12.1)	3 (8.3)	6 (8.3)	9 (8.3)
No			13 (86.7)	29 (87.9)	33 (91.7)	66 (91.7)	99 (91.7)
Duration of edaravone use (days)			2 (100)	4 (100)	3 (100)	6 (100)	9 (100)
< 60			[redacted]		[redacted]		1 (11.1)
>= 60							8 (88.9)
Edaravone and riluzole use (a)			2 (13.3)	4 (12.1)	3 (8.3)	6 (8.3)	9 (8.3)

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NOTE 5: Pre-randomization ALSFRS slope is calculated using the (ALSFRS-R score at baseline (Day 1) - maximum possible score of 48)/duration of symptom onset, where duration of symptom onset is calculated as (date of baseline ALSFRS-R score - date of symptom onset)/30.4375.
NOTE 6: Partial date with missing day is imputed with 15th of the month and partial date with missing month/day is imputed with January 15th for the calculations.
NOTE 7: King's staging is based on clinical milestones that consider involvement of 1-3 anatomical regions of bulbar region, upper limbs and lower limbs (Stage 1 = 1 region, Stage 2 = 2 regions, Stage 3 = 3 regions), the need for gastrostomy (Stage 4a), non-invasive ventilations (Stage 4b) and death (Stage 5); the higher stage takes precedence and is assigned to the subject.
(a) Numbers in parentheses are percentages and calculated based on the number of subjects in each treatment group.
Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; SOD1 = superoxide dismutase 1.
Source: biib067/233as101-partc/csr/t-als-hist.sas **Run Date:** 22SEP2021

233AS101 Part C: ALS disease history - by population

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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
ALS Milano-Torinos Staging (MITOS) at baseline	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Stage 0 [no loss on any domain]	[redacted]		[redacted]		[redacted]		81 (75.0)
Stage 1 [1 functional domain lost]							23 (21.3)
Stage 2 [2 functional domains lost]							3 (2.8)
Stage 3 [3 functional domains lost]							1 (0.9)
Stage 4 [4 functional domains lost]							0
Stage 5 [death]							0

NOTE 1: Protocol defined mutation includes p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly.
NOTE 2: Time since ALS symptom onset is calculated in months as (date of baseline ALSFRS-R score - date of ALS symptom onset)/30.4375.
NOTE 3: Subjects who have more than one site of onset are summarized under 'Multiple sites'.
NOTE 4: Time since ALS diagnosis is calculated in months as (date of baseline ALSFRS-R score - date of ALS diagnosis)/30.4375.
NOTE 5: Pre-randomization ALSFRS slope is calculated using the (ALSFRS-R score at baseline (Day 1) - maximum possible score of 48)/duration of symptom onset, where duration of symptom onset is calculated as (date of baseline ALSFRS-R score - date of symptom onset)/30.4375.
NOTE 6: Partial date with missing day is imputed with 15th of the month and partial date with missing month/day is imputed with January 15th for the calculations.
NOTE 7: King's staging is based on clinical milestones that consider involvement of 1-3 anatomical regions of bulbar region, upper limbs and lower limbs (Stage 1 = 1 region, Stage 2 = 2 regions, Stage 3 = 3 regions), the need for gastrostomy (Stage 4a), non-invasive ventilations (Stage 4b) and death (Stage 5); the higher stage takes precedence and is assigned to the subject.
(a) Numbers in parentheses are percentages and calculated based on the number of subjects in each treatment group.
Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; SOD1 = superoxide dismutase 1.
Source: biib067/233as101-partc/csr/t-als-hist.sas **Run Date:** 22SEP2021

233AS101 Part C: ALS disease history - by population

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	mITT population		non mITT population		ITT population		
	placebo (N=21)	tofersen 100 mg (N=39)	placebo (N=15)	tofersen 100 mg (N=33)	placebo (N=36)	tofersen 100 mg (N=72)	Total (N=108)
King's stage at baseline	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)	108 (100)
Stage 0 [not reached stage 1 yet]	[redacted]		[redacted]		[redacted]		1 (0.9)
Stage 1 [1 region involved]							28 (25.9)
Stage 2 [2 regions involved]							43 (39.8)
Stage 3 [3 regions involved]							25 (23.1)
Stage 4a [nutritional failure]							1 (0.9)
Stage 4b [respiratory failure]							10 (9.3)
Stage 5 [death]							0

NOTE 1: Protocol defined mutation includes p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly.
NOTE 2: Time since ALS symptom onset is calculated in months as (date of baseline ALSFRS-R score - date of ALS symptom onset)/30.4375.
NOTE 3: Subjects who have more than one site of onset are summarized under 'Multiple sites'.
NOTE 4: Time since ALS diagnosis is calculated in months as (date of baseline ALSFRS-R score - date of ALS diagnosis)/30.4375.
NOTE 5: Pre-randomization ALSFRS slope is calculated using the (ALSFRS-R score at baseline (Day 1) - maximum possible score of 48)/duration of symptom onset, where duration of symptom onset is calculated as (date of baseline ALSFRS-R score - date of symptom onset)/30.4375.
NOTE 6: Partial date with missing day is imputed with 15th of the month and partial date with missing month/day is imputed with January 15th for the calculations.
NOTE 7: King's staging is based on clinical milestones that consider involvement of 1-3 anatomical regions of bulbar region, upper limbs and lower limbs (Stage 1 = 1 region, Stage 2 = 2 regions, Stage 3 = 3 regions), the need for gastrostomy (Stage 4a), non-invasive ventilations (Stage 4b) and death (Stage 5); the higher stage takes precedence and is assigned to the subject.
(a) Numbers in parentheses are percentages and calculated based on the number of subjects in each treatment group.
Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; SOD1 = superoxide dismutase 1.
Source: biib067/233as101-partc/csr/t-als-hist.sas **Run Date:** 22SEP2021

233AS101 Part C: Secondary endpoint analysis: Summary of time to death or permanent ventilation - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with an event of death or permanent ventilation	2 (5.6)	4 (5.6)
Death	0	1 (1.4)
Permanent ventilation	2 (5.6)	3 (4.2)
Number of days with ventilation use for at least 22 hours per day		
n	2	3
Mean (SD)	15.0 (18.38)	20.0 (18.52)
Median	15.0	21.0
Q1,Q3	2.0, 28.0	1.0, 38.0
Min, Max	2, 28	1, 38
[redacted]		
Number of subjects who were censored	34 (94.4)	68 (94.4)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/233as101-partc/csr/t-cf-vafs-sum.sas:t-cf-vafs-sum-itt.rtf **Run Date:** 22SEP2021

233AS101 Part C: Secondary endpoint analysis: Summary of time to death or permanent ventilation - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	196.0 (NE, NE)
10th percentile	NE (171.0, NE)	NE (114.0, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.061	0.062
p-value (tofersen - placebo) (b)		0.9249
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.97 (0.166, 5.709)
p-value (tofersen - placebo) (c)		0.9772

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/233as101-partc/csr/t-cf-vafs-sum.sas:t-cf-vafs-sum-itt.rtf **Run Date:** 22SEP2021

233AS101 Part C: Secondary endpoint secondary analysis: Kaplan-Meier plot of time to death or permanent ventilation - ITT population

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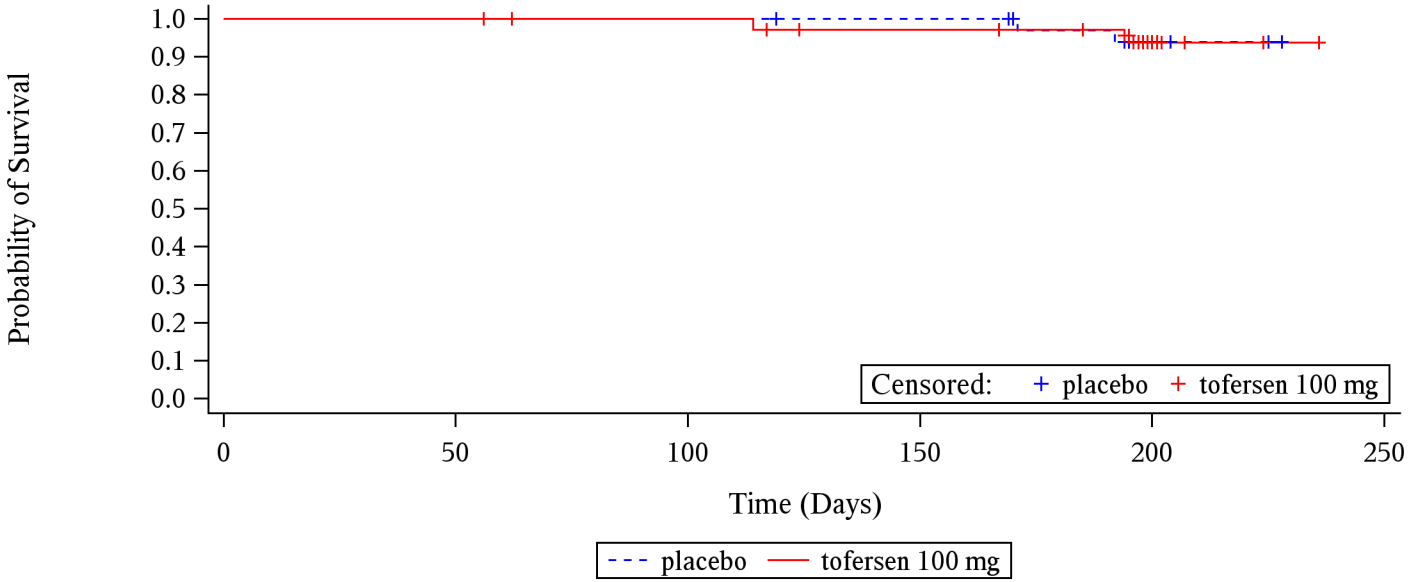

At Risk:						
placebo	36	36	36	35	5	0
tofersen 100 mg	72	72	70	66	7	0

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
NOTE 2: + indicates censored data.
Abbreviations: EAC = Endpoint Adjudication Committee.
Source: biib067/233as101-partc/csr/f-vafs-km.sas:f-vafs-km-itt.rtf **Run Date:** 22SEP2021

233AS101 Part C: Secondary endpoint analysis: Summary of time to death - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects who died	0	1 (1.4)
Number of subjects who were censored	36 (100)	71 (98.6)
Time to death (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	NE (NE, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)
Estimated proportion (a) of subjects who died by 197 days	NE	NE
p-value (tofersen vs. placebo) (b)		NE
Hazard ratio (tofersen vs. placebo) and 95% CI (c)		NE (NE, NE)
p-value (tofersen vs. placebo) (c)		NE

NOTE 1: Time to death is defined as the time from first dose to death. Subjects who are still alive are censored on the latest of the date of last follow-up or Day 197 visit date.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: NE = not estimable.
Source: biib067/233as101-partc/csr/t-surv-sum.sas:t-surv-sum-itt.rtf **Run Date:** 22SEP2021

233AS101 Part C: Secondary endpoint secondary analysis: Kaplan-Meier plot of time to death - ITT population

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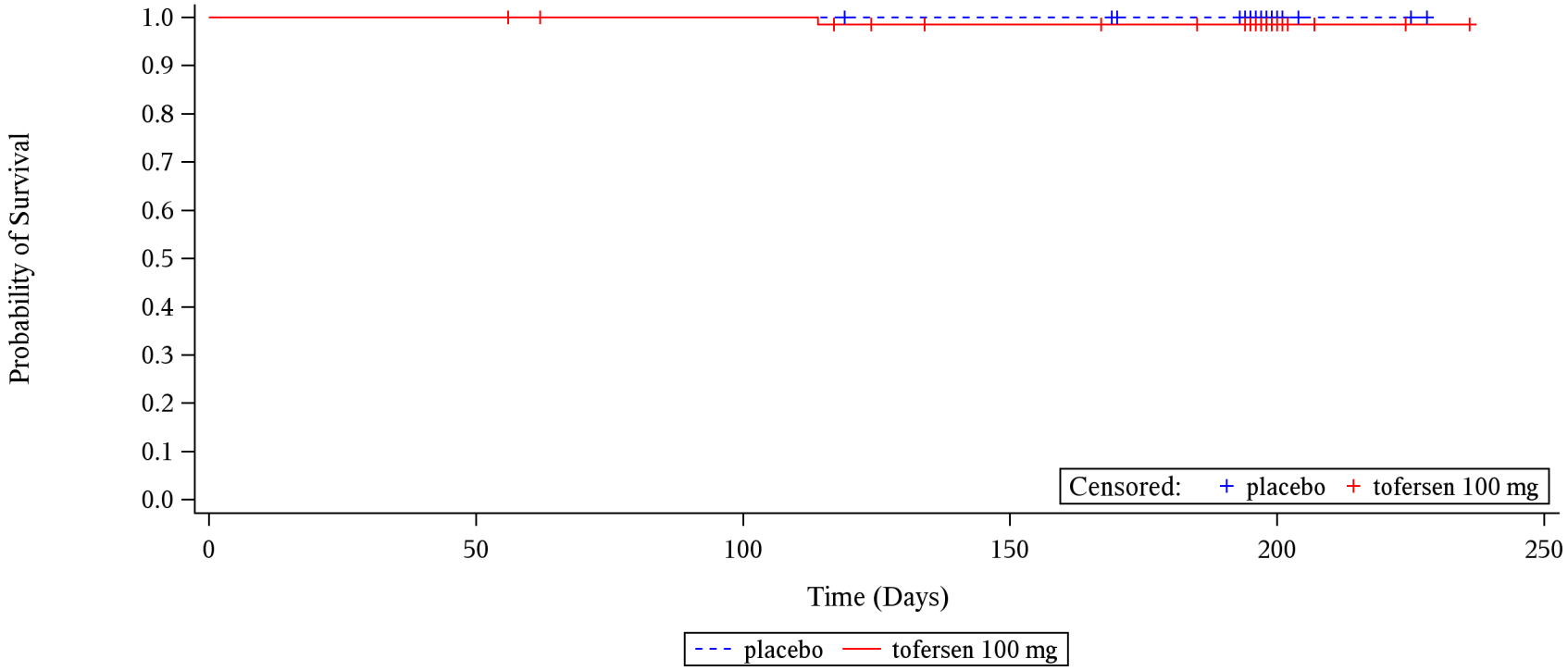

At Risk:						
placebo	36	36	36	35	5	0
tofersen 100 mg	72	72	70	66	7	0

NOTE 1: Time to death is defined as the time from first dose to death. Subjects who are still alive are censored on the latest of the date of last follow-up or Day 197 visit date.
NOTE 2: + indicates censored data.
Source: biib067/233as101-partc/csr/f-surv-km.sas:f-surv-km-itt.rtf **Run Date:** 22SEP2021

233AS101 Part C: Summary of time to permanent ventilation - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with permanent ventilation	2 (5.6)	3 (4.2)
Number of subjects who were censored	34 (94.4)	69 (95.8)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	NE (114.0, NE)
10th percentile	NE (171.0, NE)	NE (194.0, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to permanent ventilation - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.061	0.048
p-value (tofersen - placebo) (b)		0.8218
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.82 (0.125, 5.341)
p-value (tofersen - placebo) (c)		0.8332

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Kaplan-Meier plot of time to permanent ventilation - ITT population

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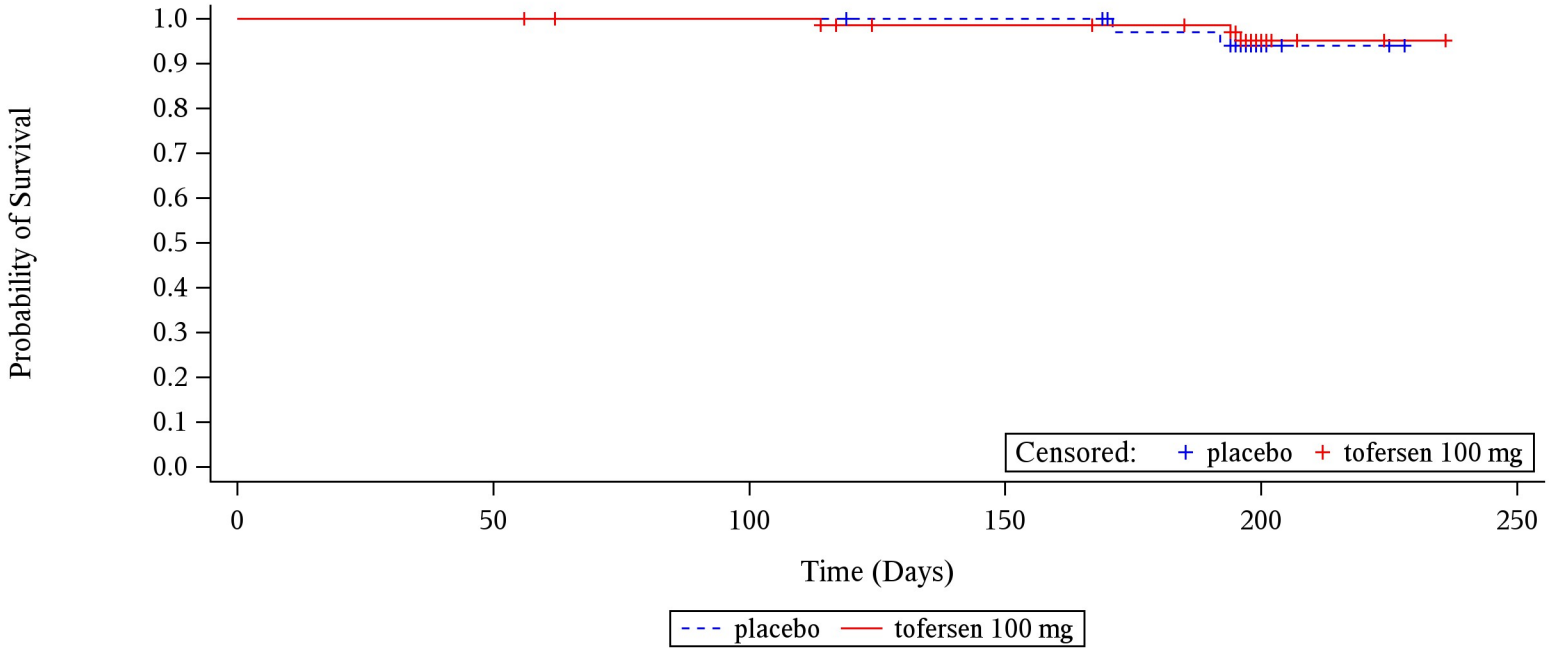

At Risk:						
placebo	36	36	36	35	5	0
tofersen 100 mg	72	72	70	66	7	0

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
NOTE 2: + indicates censored data.
Source: biib067/valueaccess/amnog/f-surv-km-vafsp-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	-0.3
SE	0.35	0.27
95% CI	(-0.78, 0.59)	(-0.86, 0.20)
LS mean difference (tofersen - placebo)		-0.2
SE		0.38
95% CI		(-0.98, 0.51)
p-value		0.5337
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.29)
p-value		0.5877

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	-0.3
SE	0.38	0.30
95% CI	(-0.89, 0.60)	(-0.88, 0.29)
LS mean difference (tofersen - placebo)		-0.1
SE		0.41
95% CI		(-0.95, 0.66)
p-value		0.7195
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.47, 0.33)
p-value		0.7279

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	35 (97.2)	70 (97.2)
Number of imputed values per imputation	1 (2.8)	2 (2.8)
LS mean change from baseline	-0.5	-0.8
SE	0.49	0.39
95% CI	(-1.47, 0.46)	(-1.53, -0.02)
LS mean difference (tofersen - placebo)		-0.3
SE		0.54
95% CI		(-1.32, 0.78)
p-value		0.6158
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.32)
p-value		0.6817

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-1.8	-1.5
SE	0.67	0.54
95% CI	(-3.16, -0.54)	(-2.52, -0.42)
LS mean difference (tofersen - placebo)		0.4
SE		0.73
95% CI		(-1.06, 1.81)
p-value		0.6057
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.29, 0.52)
p-value		0.5870

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	35 (97.2)	67 (93.1)
Number of imputed values per imputation	1 (2.8)	5 (6.9)
LS mean change from baseline	-2.9	-2.3
SE	0.99	0.79
95% CI	(-4.79, -0.91)	(-3.85, -0.77)
LS mean difference (tofersen - placebo)		0.5
SE		1.08
95% CI		(-1.57, 2.66)
p-value		0.6137
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.30, 0.52)
p-value		0.5963

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-3.3	-2.9
SE	1.01	0.80
95% CI	(-5.27, -1.31)	(-4.47, -1.31)
LS mean difference (tofersen - placebo)		0.4
SE		1.11
95% CI		(-1.77, 2.57)
p-value		0.7169
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.33, 0.50)
p-value		0.6994

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-4.4	-3.4
SE	1.11	0.88
95% CI	(-6.58, -2.24)	(-5.16, -1.71)
LS mean difference (tofersen - placebo)		1.0
SE		1.21
95% CI		(-1.40, 3.35)
p-value		0.4209
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.24, 0.59)
p-value		0.4061

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-5.8	-4.5
SE	1.27	1.01
95% CI	(-8.31, -3.35)	(-6.43, -2.48)
LS mean difference (tofersen - placebo)		1.4
SE		1.39
95% CI		(-1.34, 4.09)
p-value		0.3218
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.21, 0.63)
p-value		0.3271

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-alsf-byvis-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	0.0	0.2
SE	0.11	0.08
95% CI	(-0.18, 0.24)	(-0.01, 0.32)
LS mean difference (tofersen - placebo)		0.1
SE		0.12
95% CI		(-0.11, 0.35)
p-value		0.3139
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.26, 0.55)
p-value		0.4756

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	0.2	0.1
SE	0.12	0.09
95% CI	(-0.07, 0.39)	(-0.06, 0.29)
LS mean difference (tofersen - placebo)		0.0
SE		0.13
95% CI		(-0.29, 0.20)
p-value		0.7182
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.31)
p-value		0.6512

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	35 (97.2)	70 (97.2)
Number of imputed values per imputation	1 (2.8)	2 (2.8)
LS mean change from baseline	-0.2	-0.1
SE	0.14	0.11
95% CI	(-0.45, 0.09)	(-0.31, 0.12)
LS mean difference (tofersen - placebo)		0.1
SE		0.15
95% CI		(-0.22, 0.38)
p-value		0.5927
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.31, 0.50)
p-value		0.6333

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	0.0
SE	0.16	0.13
95% CI	(-0.46, 0.19)	(-0.28, 0.23)
LS mean difference (tofersen - placebo)		0.1
SE		0.18
95% CI		(-0.25, 0.46)
p-value		0.5484
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.28, 0.53)
p-value		0.5390

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	35 (97.2)	67 (93.1)
Number of imputed values per imputation	1 (2.8)	5 (6.9)
LS mean change from baseline	-0.1	-0.4
SE	0.21	0.16
95% CI	(-0.53, 0.27)	(-0.69, -0.05)
LS mean difference (tofersen - placebo)		-0.2
SE		0.23
95% CI		(-0.68, 0.20)
p-value		0.2852
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.60, 0.22)
p-value		0.3614

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-0.1	-0.6
SE	0.24	0.19
95% CI	(-0.61, 0.33)	(-0.94, -0.19)
LS mean difference (tofersen - placebo)		-0.4
SE		0.26
95% CI		(-0.95, 0.09)
p-value		0.1074
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.71, 0.13)
p-value		0.1712

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-0.5	-0.5
SE	0.23	0.19
95% CI	(-0.97, -0.05)	(-0.83, -0.10)
LS mean difference (tofersen - placebo)		0.0
SE		0.26
95% CI		(-0.46, 0.55)
p-value		0.8685
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.36, 0.47)
p-value		0.8075

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-0.4	-0.7
SE	0.27	0.22
95% CI	(-0.98, 0.09)	(-1.13, -0.27)
LS mean difference (tofersen - placebo)		-0.3
SE		0.30
95% CI		(-0.85, 0.33)
p-value		0.3950
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.57, 0.28)
p-value		0.4957

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

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ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	0.0	-0.1
SE	0.16	0.13
95% CI	(-0.31, 0.33)	(-0.33, 0.16)
LS mean difference (tofersen - placebo)		-0.1
SE		0.18
95% CI		(-0.44, 0.25)
p-value		0.5900
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.32)
p-value		0.6891

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	0.0	-0.2
SE	0.15	0.12
95% CI	(-0.29, 0.30)	(-0.38, 0.08)
LS mean difference (tofersen - placebo)		-0.2
SE		0.16
95% CI		(-0.47, 0.17)
p-value		0.3437
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.59, 0.22)
p-value		0.3708

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	35 (97.2)	70 (97.2)
Number of imputed values per imputation	1 (2.8)	2 (2.8)
LS mean change from baseline	-0.1	-0.4
SE	0.23	0.18
95% CI	(-0.56, 0.32)	(-0.70, -0.01)
LS mean difference (tofersen - placebo)		-0.2
SE		0.24
95% CI		(-0.71, 0.24)
p-value		0.3381
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.57, 0.24)
p-value		0.4238

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.6	-0.6
SE	0.25	0.20
95% CI	(-1.04, -0.07)	(-1.01, -0.24)
LS mean difference (tofersen - placebo)		-0.1
SE		0.27
95% CI		(-0.60, 0.46)
p-value		0.7994
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.44, 0.38)
p-value		0.8832

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	35 (97.2)	67 (93.1)
Number of imputed values per imputation	1 (2.8)	5 (6.9)
LS mean change from baseline	-0.7	-0.9
SE	0.30	0.24
95% CI	(-1.29, -0.11)	(-1.33, -0.40)
LS mean difference (tofersen - placebo)		-0.2
SE		0.33
95% CI		(-0.81, 0.48)
p-value		0.6166
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.48, 0.33)
p-value		0.7157

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-0.9	-0.9
SE	0.33	0.26
95% CI	(-1.55, -0.27)	(-1.41, -0.40)
LS mean difference (tofersen - placebo)		0.0
SE		0.36
95% CI		(-0.69, 0.70)
p-value		0.9898
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.39, 0.44)
p-value		0.8912

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-1.2	-1.1
SE	0.36	0.28
95% CI	(-1.88, -0.49)	(-1.62, -0.52)
LS mean difference (tofersen - placebo)		0.1
SE		0.39
95% CI		(-0.64, 0.87)
p-value		0.7693
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.32, 0.50)
p-value		0.6694

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-2.0	-1.3
SE	0.42	0.33
95% CI	(-2.80, -1.16)	(-1.99, -0.70)
LS mean difference (tofersen - placebo)		0.6
SE		0.46
95% CI		(-0.26, 1.53)
p-value		0.1666
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.13, 0.72)
p-value		0.1674

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	-0.2
SE	0.15	0.12
95% CI	(-0.35, 0.23)	(-0.45, 0.01)
LS mean difference (tofersen - placebo)		-0.2
SE		0.16
95% CI		(-0.48, 0.16)
p-value		0.3176
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.61, 0.20)
p-value		0.3157

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.2	-0.1
SE	0.20	0.16
95% CI	(-0.62, 0.16)	(-0.45, 0.15)
LS mean difference (tofersen - placebo)		0.1
SE		0.21
95% CI		(-0.34, 0.50)
p-value		0.7084
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.32, 0.48)
p-value		0.7051

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

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ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	35 (97.2)	70 (97.2)
Number of imputed values per imputation	1 (2.8)	2 (2.8)
LS mean change from baseline	-0.2	-0.2
SE	0.24	0.19
95% CI	(-0.72, 0.23)	(-0.59, 0.16)
LS mean difference (tofersen - placebo)		0.0
SE		0.26
95% CI		(-0.48, 0.55)
p-value		0.9002
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.36, 0.45)
p-value		0.8194

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	[redacted]
Number of imputed values per imputation	[redacted]	[redacted]
LS mean change from baseline	-0.7	-0.6
SE	0.26	0.20
95% CI	(-1.16, -0.15)	(-0.99, -0.19)
LS mean difference (tofersen - placebo)		0.1
SE		0.28
95% CI		(-0.48, 0.61)
p-value		0.8128
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.34, 0.47)
p-value		0.7494

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	35 (97.2)	67 (93.1)
Number of imputed values per imputation	1 (2.8)	5 (6.9)
LS mean change from baseline	-1.1	-0.7
SE	0.31	0.24
95% CI	(-1.72, -0.51)	(-1.17, -0.21)
LS mean difference (tofersen - placebo)		0.4
SE		0.34
95% CI		(-0.23, 1.08)
p-value		0.2065
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.14, 0.68)
p-value		0.2001

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-1.4	-0.8
SE	0.32	0.26
95% CI	(-2.01, -0.75)	(-1.27, -0.27)
LS mean difference (tofersen - placebo)		0.6
SE		0.35
95% CI		(-0.09, 1.30)
p-value		0.0857
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.07, 0.76)
p-value		0.1046

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-1.6	-0.9
SE	0.34	0.27
95% CI	(-2.24, -0.93)	(-1.47, -0.43)
LS mean difference (tofersen - placebo)		0.6
SE		0.37
95% CI		(-0.08, 1.35)
p-value		0.0810
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.05, 0.79)
p-value		0.0825

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-1.9	-1.0
SE	0.38	0.30
95% CI	(-2.60, -1.13)	(-1.61, -0.44)
LS mean difference (tofersen - placebo)		0.8
SE		0.41
95% CI		(0.04, 1.65)
p-value		0.0403
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(0.00, 0.85)
p-value		0.0487

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	[redacted]	[redacted]
Number of imputed values per imputation	[redacted]	[redacted]
LS mean change from baseline	-0.1	-0.2
SE	0.20	0.16
95% CI	(-0.48, 0.31)	(-0.46, 0.16)
LS mean difference (tofersen - placebo)		-0.1
SE		0.22
95% CI		(-0.49, 0.36)
p-value		0.7561
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.46, 0.35)
p-value		0.7835

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	-0.1
SE	0.19	0.15
95% CI	(-0.46, 0.31)	(-0.39, 0.21)
LS mean difference (tofersen - placebo)		0.0
SE		0.21
95% CI		(-0.43, 0.39)
p-value		0.9287
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.42, 0.38)
p-value		0.9231

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	35 (97.2)	70 (97.2)
Number of imputed values per imputation	1 (2.8)	2 (2.8)
LS mean change from baseline	0.0	-0.1
SE	0.22	0.17
95% CI	(-0.39, 0.48)	(-0.45, 0.23)
LS mean difference (tofersen - placebo)		-0.2
SE		0.24
95% CI		(-0.63, 0.32)
p-value		0.5175
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.54, 0.27)
p-value		0.5210

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

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ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.5	-0.2
SE	0.35	0.28
95% CI	(-1.18, 0.21)	(-0.78, 0.32)
LS mean difference (tofersen - placebo)		0.3
SE		0.39
95% CI		(-0.50, 1.01)
p-value		0.5130
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.28, 0.54)
p-value		0.5291

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	35 (97.2)	67 (93.1)
Number of imputed values per imputation	1 (2.8)	5 (6.9)
LS mean change from baseline	-0.9	-0.4
SE	0.45	0.35
95% CI	(-1.74, 0.00)	(-1.09, 0.29)
LS mean difference (tofersen - placebo)		0.5
SE		0.49
95% CI		(-0.48, 1.42)
p-value		0.3308
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.21, 0.61)
p-value		0.3398

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-0.8	-0.7
SE	0.42	0.34
95% CI	(-1.65, 0.02)	(-1.31, 0.01)
LS mean difference (tofersen - placebo)		0.2
SE		0.46
95% CI		(-0.75, 1.07)
p-value		0.7258
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.34, 0.49)
p-value		0.7139

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-1.1	-1.0
SE	0.51	0.41
95% CI	(-2.10, -0.08)	(-1.76, -0.17)
LS mean difference (tofersen - placebo)		0.1
SE		0.56
95% CI		(-0.98, 1.23)
p-value		0.8228
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.36, 0.46)
p-value		0.8117

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSFRS-R domain score change from baseline by visit ANCOVA analysis using MI - ITT population

ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-1.5	-1.4
SE	0.55	0.43
95% CI	(-2.55, -0.41)	(-2.26, -0.56)
LS mean difference (tofersen - placebo)		0.1
SE		0.60
95% CI		(-1.10, 1.25)
p-value		0.9025
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.39, 0.45)
p-value		0.8804

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-alsf-anc-mi-chg.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	27.8	25.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.95
SE of log(RR)		0.348
95% CI		(0.478, 1.872)
p-value		0.8743
Adjusted OR - Odds Ratio (tofersen/placebo)		0.93
SE of log(OR)		0.485
95% CI		(0.358, 2.395)
p-value		0.8738
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.094
95% CI		(-0.210, 0.160)
p-value		0.7909

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	16.9	14.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.88
SE of log(RR)		0.471
95% CI		(0.350, 2.219)
p-value		0.7887
Adjusted OR - Odds Ratio (tofersen/placebo)		0.86
SE of log(OR)		0.574
95% CI		(0.279, 2.647)
p-value		0.7924
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.076
95% CI		(-0.174, 0.124)
p-value		0.7396

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-prop-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	47.4	35.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.77
SE of log(RR)		0.234
95% CI		(0.489, 1.224)
p-value		0.2737
Adjusted OR - Odds Ratio (tofersen/placebo)		0.62
SE of log(OR)		0.442
95% CI		(0.262, 1.485)
p-value		0.2863
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.102
95% CI		(-0.320, 0.081)
p-value		0.2440

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-prop-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	44.3	37.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.87
SE of log(RR)		0.246
95% CI		(0.538, 1.410)
p-value		0.5749
Adjusted OR - Odds Ratio (tofersen/placebo)		0.79
SE of log(OR)		0.426
95% CI		(0.343, 1.823)
p-value		0.5815
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.102
95% CI		(-0.269, 0.132)
p-value		0.5036

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-prop-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

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ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	25.1	29.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.25
SE of log(RR)		0.336
95% CI		(0.644, 2.407)
p-value		0.5146
Adjusted OR - Odds Ratio (tofersen/placebo)		1.38
SE of log(OR)		0.490
95% CI		(0.530, 3.612)
p-value		0.5072
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.092
95% CI		(-0.135, 0.227)
p-value		0.6182

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-prop-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSFRS-R total score > = 15%	0.06	0.35
Adjusted RR - Relative Risk (tofersen/placebo)		0.60
SE of log(RR)		0.780
95% CI		(0.130, 2.761)
p-value		0.5104
Adjusted OR - Odds Ratio (tofersen/placebo)		0.57
SE of log(OR)		0.856
95% CI		(0.107, 3.055)
p-value		0.5122
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.024
95% CI		(-0.051, 0.043)
p-value		0.8751

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-propim-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 19JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Bulbar Function Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	11.5	0.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.22
SE of log(RR)		0.726
95% CI		(0.053, 0.914)
p-value		0.0371
Adjusted OR - Odds Ratio (tofersen/placebo)		0.18
SE of log(OR)		0.791
95% CI		(0.037, 0.832)
p-value		0.0283
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.056
95% CI		(-0.227, -0.007)
p-value		0.0372

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: The subjects with zero total score at baseline are considered as improvement if their total scores have any increase at Week 28.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	2.9	3.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.15
SE of log(RR)		1.167
95% CI		(0.116, 11.290)
p-value		0.9068
Adjusted OR - Odds Ratio (tofersen/placebo)		1.15
SE of log(OR)		1.195
95% CI		(0.110, 11.931)
p-value		0.9082
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.036
95% CI		(-0.066, 0.077)
p-value		0.8847

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: The subjects with zero total score at baseline are considered as improvement if their total scores have any increase at Week 28.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	2.9	4.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.53
SE of log(RR)		1.039
95% CI		(0.200, 11.738)
p-value		0.6814
Adjusted OR - Odds Ratio (tofersen/placebo)		1.71
SE of log(OR)		1.305
95% CI		(0.132, 22.036)
p-value		0.6823
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.037
95% CI		(-0.059, 0.087)
p-value		0.7029

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: The subjects with zero total score at baseline are considered as improvement if their total scores have any increase at Week 28.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 28 using MI - ITT population

ALSFRS-R Respiratory Domain Score

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	9.6	3.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.39
SE of log(RR)		0.865
95% CI		(0.072, 2.127)
p-value		0.2768
Adjusted OR - Odds Ratio (tofersen/placebo)		0.38
SE of log(OR)		0.878
95% CI		(0.068, 2.130)
p-value		0.2719
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.057
95% CI		(-0.169, 0.054)
p-value		0.3106

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: The subjects with zero total score at baseline are considered as improvement if their total scores have any increase at Week 28.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	33 (91.7)	71 (98.6)
Number of imputed values per imputation	3 (8.3)	1 (1.4)
LS mean change from baseline	-0.01	-0.01
SE	0.038	0.029
95% CI	(-0.079, 0.069)	(-0.069, 0.044)
LS mean difference (tofersen - placebo)		-0.01
SE		0.040
95% CI		(-0.085, 0.071)
p-value		0.8601
Hedge's g standardized mean difference (tofersen - placebo)		-0.02
95% CI		(-0.438, 0.388)
p-value		0.9062

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	33 (91.7)	70 (97.2)
Number of imputed values per imputation	3 (8.3)	2 (2.8)
LS mean change from baseline	-0.03	-0.08
SE	0.046	0.035
95% CI	(-0.118, 0.061)	(-0.149, -0.012)
LS mean difference (tofersen - placebo)		-0.05
SE		0.048
95% CI		(-0.146, 0.042)
p-value		0.2797
Hedge's g standardized mean difference (tofersen - placebo)		-0.20
95% CI		(-0.611, 0.219)
p-value		0.3544

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	31 (86.1)	65 (90.3)
Number of imputed values per imputation	5 (13.9)	7 (9.7)
LS mean change from baseline	-0.10	-0.10
SE	0.052	0.040
95% CI	(-0.204, 0.000)	(-0.176, -0.021)
LS mean difference (tofersen - placebo)		0.00
SE		0.055
95% CI		(-0.105, 0.112)
p-value		0.9486
Hedge's g standardized mean difference (tofersen - placebo)		0.04
95% CI		(-0.390, 0.466)
p-value		0.8619

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	35 (97.2)	64 (88.9)
Number of imputed values per imputation	1 (2.8)	8 (11.1)
LS mean change from baseline	-0.15	-0.12
SE	0.054	0.043
95% CI	(-0.259, -0.045)	(-0.202, -0.032)
LS mean difference (tofersen - placebo)		0.04
SE		0.059
95% CI		(-0.081, 0.152)
p-value		0.5505
Hedge's g standardized mean difference (tofersen - placebo)		0.14
95% CI		(-0.272, 0.553)
p-value		0.5034

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-0.15	-0.13
SE	0.063	0.050
95% CI	(-0.276, -0.028)	(-0.226, -0.030)
LS mean difference (tofersen - placebo)		0.02
SE		0.069
95% CI		(-0.110, 0.159)
p-value		0.7213
Hedge's g standardized mean difference (tofersen - placebo)		0.09
95% CI		(-0.333, 0.510)
p-value		0.6804

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	30 (83.3)	63 (87.5)
Number of imputed values per imputation	6 (16.7)	9 (12.5)
LS mean change from baseline	-0.23	-0.14
SE	0.064	0.051
95% CI	(-0.351, -0.099)	(-0.243, -0.044)
LS mean difference (tofersen - placebo)		0.08
SE		0.070
95% CI		(-0.055, 0.218)
p-value		0.2431
Hedge's g standardized mean difference (tofersen - placebo)		0.26
95% CI		(-0.173, 0.700)
p-value		0.2363

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	31 (86.1)	62 (86.1)
Number of imputed values per imputation	5 (13.9)	10 (13.9)
LS mean change from baseline	-0.30	-0.16
SE	0.070	0.055
95% CI	(-0.442, -0.168)	(-0.264, -0.049)
LS mean difference (tofersen - placebo)		0.15
SE		0.076
95% CI		(-0.001, 0.298)
p-value		0.0521
Hedge's g standardized mean difference (tofersen - placebo)		0.42
95% CI		(-0.013, 0.858)
p-value		0.0574

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: HHD overall megascore change from baseline by visit ANCOVA analysis using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	27 (75.0)	58 (80.6)
Number of imputed values per imputation	9 (25.0)	14 (19.4)
LS mean change from baseline	-0.29	-0.23
SE	0.070	0.055
95% CI	(-0.425, -0.150)	(-0.336, -0.121)
LS mean difference (tofersen - placebo)		0.06
SE		0.077
95% CI		(-0.092, 0.211)
p-value		0.4416
Hedge's g standardized mean difference (tofersen - placebo)		0.19
95% CI		(-0.267, 0.649)
p-value		0.4134

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-phoc-mega-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 15		
Number of observations per imputation	32 (88.9)	67 (93.1)
Number of imputed values per imputation	4 (11.1)	5 (6.9)
LS mean change from baseline	0.27	0.04
SE	1.475	1.127
95% CI	(-2.621, 3.161)	(-2.166, 2.253)
LS mean difference (tofersen - placebo)		-0.23
SE		1.567
95% CI		(-3.298, 2.846)
p-value		0.8854
Hedge's g standardized mean difference (tofersen - placebo)		-0.02
95% CI		(-0.439, 0.403)
p-value		0.9331

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29		
Number of observations per imputation	31 (86.1)	66 (91.7)
Number of imputed values per imputation	5 (13.9)	6 (8.3)
LS mean change from baseline	-1.03	-1.01
SE	1.488	1.126
95% CI	(-3.945, 1.890)	(-3.216, 1.196)
LS mean difference (tofersen - placebo)		0.02
SE		1.586
95% CI		(-3.091, 3.126)
p-value		0.9913
Hedge's g standardized mean difference (tofersen - placebo)		-0.01
95% CI		(-0.432, 0.422)
p-value		0.9809

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	30 (83.3)	62 (86.1)
Number of imputed values per imputation	6 (16.7)	10 (13.9)
LS mean change from baseline	-3.68	-2.50
SE	1.661	1.255
95% CI	(-6.938, -0.427)	(-4.960, -0.039)
LS mean difference (tofersen - placebo)		1.18
SE		1.799
95% CI		(-2.344, 4.709)
p-value		0.5109
Hedge's g standardized mean difference (tofersen - placebo)		0.12
95% CI		(-0.314, 0.558)
p-value		0.5841

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	34 (94.4)	59 (81.9)
Number of imputed values per imputation	2 (5.6)	13 (18.1)
LS mean change from baseline	-6.66	-3.57
SE	1.888	1.473
95% CI	(-10.359, -2.958)	(-6.457, -0.685)
LS mean difference (tofersen - placebo)		3.09
SE		2.072
95% CI		(-0.975, 7.150)
p-value		0.1363
Hedge's g standardized mean difference (tofersen - placebo)		0.28
95% CI		(-0.148, 0.700)
p-value		0.2019

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	32 (88.9)	58 (80.6)
Number of imputed values per imputation	4 (11.1)	14 (19.4)
LS mean change from baseline	-9.31	-5.86
SE	2.308	1.797
95% CI	(-13.831, -4.783)	(-9.381, -2.337)
LS mean difference (tofersen - placebo)		3.45
SE		2.511
95% CI		(-1.473, 8.369)
p-value		0.1696
Hedge's g standardized mean difference (tofersen - placebo)		0.25
95% CI		(-0.183, 0.683)
p-value		0.2576

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	30 (83.3)	57 (79.2)
Number of imputed values per imputation	6 (16.7)	15 (20.8)
LS mean change from baseline	-11.14	-6.22
SE	2.610	2.020
95% CI	(-16.258, -6.028)	(-10.179, -2.262)
LS mean difference (tofersen - placebo)		4.92
SE		2.830
95% CI		(-0.623, 10.469)
p-value		0.0819
Hedge's g standardized mean difference (tofersen - placebo)		0.32
95% CI		(-0.130, 0.760)
p-value		0.1649

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	31 (86.1)	56 (77.8)
Number of imputed values per imputation	5 (13.9)	16 (22.2)
LS mean change from baseline	-13.50	-6.84
SE	2.965	2.299
95% CI	(-19.307, -7.684)	(-11.346, -2.333)
LS mean difference (tofersen - placebo)		6.66
SE		3.218
95% CI		(0.349, 12.962)
p-value		0.0386
Hedge's g standardized mean difference (tofersen - placebo)		0.39
95% CI		(-0.051, 0.835)
p-value		0.0826

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	25 (69.4)	52 (72.2)
Number of imputed values per imputation	11 (30.6)	20 (27.8)
LS mean change from baseline	-14.82	-7.94
SE	3.275	2.520
95% CI	(-21.244, -8.406)	(-12.883, -3.004)
LS mean difference (tofersen - placebo)		6.88
SE		3.545
95% CI		(-0.067, 13.830)
p-value		0.0522
Hedge's g standardized mean difference (tofersen - placebo)		0.37
95% CI		(-0.112, 0.849)
p-value		0.1327

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-phoc-svc-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21APR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-1.0	-3.1
SE	2.31	1.79
95% CI	(-5.50, 3.55)	(-6.63, 0.40)
LS mean difference (tofersen - placebo)		-2.1
SE		2.51
95% CI		(-7.06, 2.79)
p-value		0.3955
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.42, 0.39)
p-value		0.9529

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-8.2	-3.3
SE	2.46	1.96
95% CI	(-13.04, -3.39)	(-7.19, 0.49)
LS mean difference (tofersen - placebo)		4.9
SE		2.70
95% CI		(-0.42, 10.16)
p-value		0.0713
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(0.05, 0.89)
p-value		0.0271

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	35 (97.2)	65 (90.3)
Number of imputed values per imputation	1 (2.8)	7 (9.7)
LS mean change from baseline	-5.7	-4.3
SE	2.55	2.01
95% CI	(-10.65, -0.66)	(-8.27, -0.40)
LS mean difference (tofersen - placebo)		1.3
SE		2.78
95% CI		(-4.12, 6.76)
p-value		0.6350
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.21, 0.62)
p-value		0.3322

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	-9.8	-4.8
SE	2.71	2.12
95% CI	(-15.11, -4.47)	(-8.99, -0.68)
LS mean difference (tofersen - placebo)		5.0
SE		2.96
95% CI		(-0.85, 10.77)
p-value		0.0943
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(0.03, 0.87)
p-value		0.0359

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	-10.3	-5.9
SE	2.90	2.26
95% CI	(-16.01, -4.65)	(-10.29, -1.44)
LS mean difference (tofersen - placebo)		4.5
SE		3.17
95% CI		(-1.75, 10.68)
p-value		0.1593
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.05, 0.79)
p-value		0.0844

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	33 (91.7)	65 (90.3)
Number of imputed values per imputation	3 (8.3)	7 (9.7)
LS mean change from baseline	-12.2	-7.9
SE	3.34	2.59
95% CI	(-18.74, -5.64)	(-12.97, -2.80)
LS mean difference (tofersen - placebo)		4.3
SE		3.67
95% CI		(-2.88, 11.50)
p-value		0.2400
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.10, 0.74)
p-value		0.1331

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	-12.1	-7.8
SE	3.54	2.78
95% CI	(-19.07, -5.18)	(-13.28, -2.40)
LS mean difference (tofersen - placebo)		4.3
SE		3.87
95% CI		(-3.30, 11.88)
p-value		0.2684
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.13, 0.74)
p-value		0.1638

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: Line plot of EQ-5D-5L VAS score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

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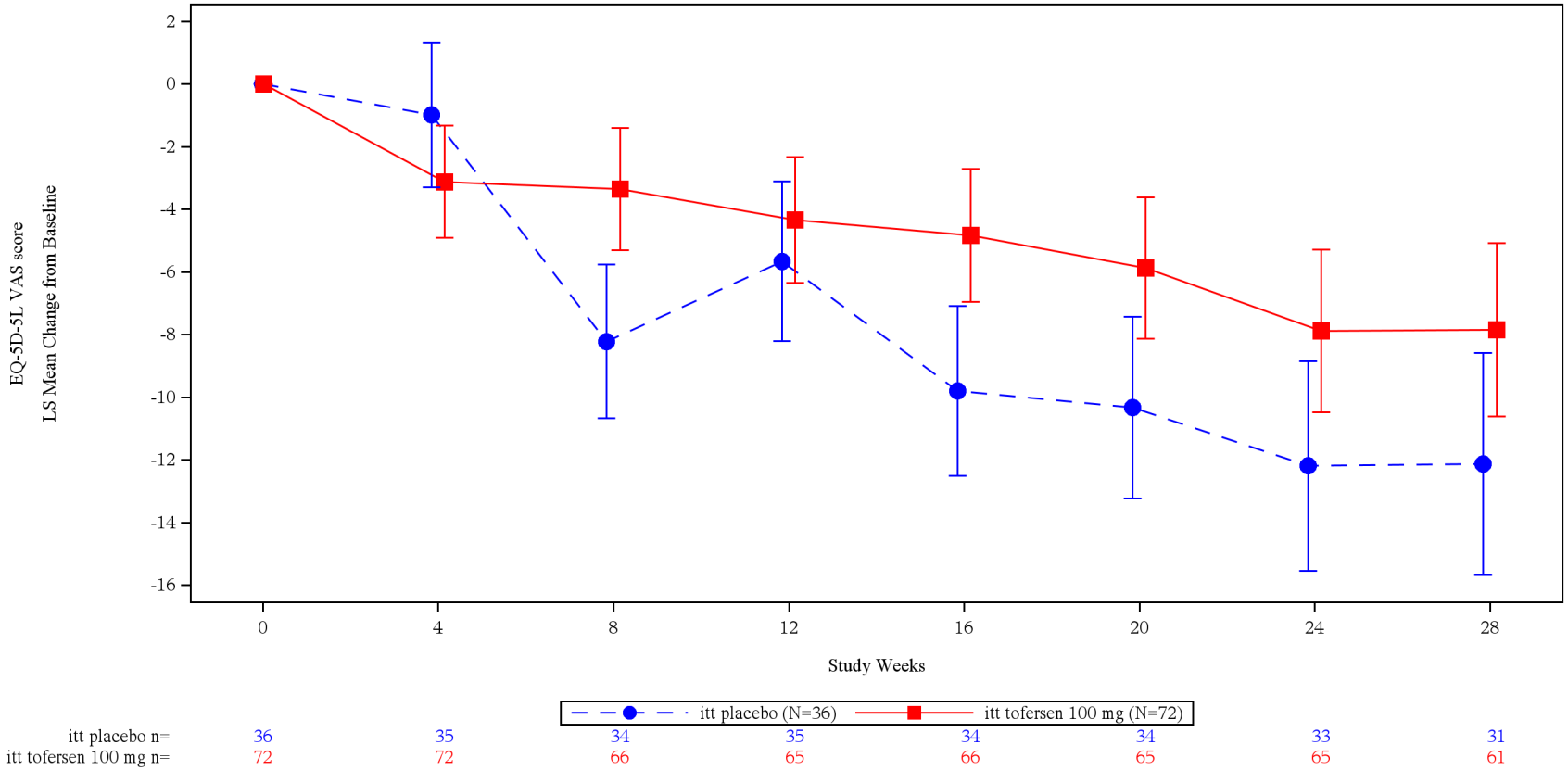

itt placebo n=	36	35	34	35	34	34	33	31
itt tofersen 100 mg n=	72	72	66	65	66	65	65	61

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-eq5vas-anc-mi-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Line plot of EQ-5D-5L VAS score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-exp-eq5vas-anc-mi-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	36.6	25.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.309
95% CI		(0.396, 1.328)
p-value		0.2981
Adjusted OR - Odds Ratio (tofersen/placebo)		0.63
SE of log(OR)		0.448
95% CI		(0.263, 1.526)
p-value		0.3088
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.097
95% CI		(-0.299, 0.083)
p-value		0.2673

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of improvement in EQ-5D VAS >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in EQ-5D VAS > = 15%	6.0	5.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.90
SE of log(RR)		0.888
95% CI		(0.158, 5.150)
p-value		0.9081
Adjusted OR - Odds Ratio (tofersen/placebo)		0.90
SE of log(OR)		0.894
95% CI		(0.156, 5.206)
p-value		0.9086
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.049
95% CI		(-0.102, 0.091)
p-value		0.9128

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of PGI-S and PGI-C response rate - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with PGI-S data, n(%)	23 (63.9)	35 (48.6)
Baseline	13/36 (36.1)	20/72 (27.8)
Day 197	21/33 (63.6)	32/65 (49.2)
Number of subjects with PGI-C data, n(%)	22 (61.1)	31 (43.1)
Day 197	22/33 (66.7)	31/65 (47.7)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Percentages in parentheses are calculated using the number of subjects who have the potential to be evaluated for the visit.
Abbreviations: PGI-S = Patient Global Impression of Status; PGI-C = Patient Global Impression of Change.
Source: biib067/valueaccess/amnog/t-cf-pgi-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 02MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	1.4	0.1
SE	1.96	1.53
95% CI	(-2.48, 5.21)	(-2.87, 3.14)
LS mean difference (tofersen - placebo)		-1.2
SE		2.12
95% CI		(-5.39, 2.93)
p-value		0.5626
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.32)
p-value		0.6879

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	33 (91.7)	70 (97.2)
Number of imputed values per imputation	3 (8.3)	2 (2.8)
LS mean change from baseline	0.4	0.1
SE	1.93	1.50
95% CI	(-3.40, 4.18)	(-2.87, 3.02)
LS mean difference (tofersen - placebo)		-0.3
SE		2.09
95% CI		(-4.42, 3.78)
p-value		0.8780
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.43, 0.40)
p-value		0.9370

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	35 (97.2)	66 (91.7)
Number of imputed values per imputation	1 (2.8)	6 (8.3)
LS mean change from baseline	1.8	0.4
SE	1.92	1.51
95% CI	(-2.01, 5.51)	(-2.52, 3.39)
LS mean difference (tofersen - placebo)		-1.3
SE		2.08
95% CI		(-5.40, 2.75)
p-value		0.5251
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.53, 0.29)
p-value		0.5744

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	1.1	1.6
SE	2.13	1.67
95% CI	(-3.02, 5.31)	(-1.70, 4.87)
LS mean difference (tofersen - placebo)		0.4
SE		2.32
95% CI		(-4.10, 4.98)
p-value		0.8499
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.37, 0.46)
p-value		0.8226

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	5.2	2.2
SE	2.22	1.76
95% CI	(0.87, 9.59)	(-1.22, 5.66)
LS mean difference (tofersen - placebo)		-3.0
SE		2.42
95% CI		(-7.76, 1.74)
p-value		0.2142
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.65, 0.18)
p-value		0.2742

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	33 (91.7)	65 (90.3)
Number of imputed values per imputation	3 (8.3)	7 (9.7)
LS mean change from baseline	4.6	2.7
SE	2.11	1.67
95% CI	(0.44, 8.73)	(-0.61, 5.92)
LS mean difference (tofersen - placebo)		-1.9
SE		2.31
95% CI		(-6.44, 2.60)
p-value		0.4041
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.57, 0.27)
p-value		0.4775

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: FSS total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	5.8	3.9
SE	2.35	1.86
95% CI	(1.14, 10.37)	(0.27, 7.56)
LS mean difference (tofersen - placebo)		-1.8
SE		2.57
95% CI		(-6.87, 3.20)
p-value		0.4742
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.56, 0.30)
p-value		0.5576

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: Line plot of FSS total score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

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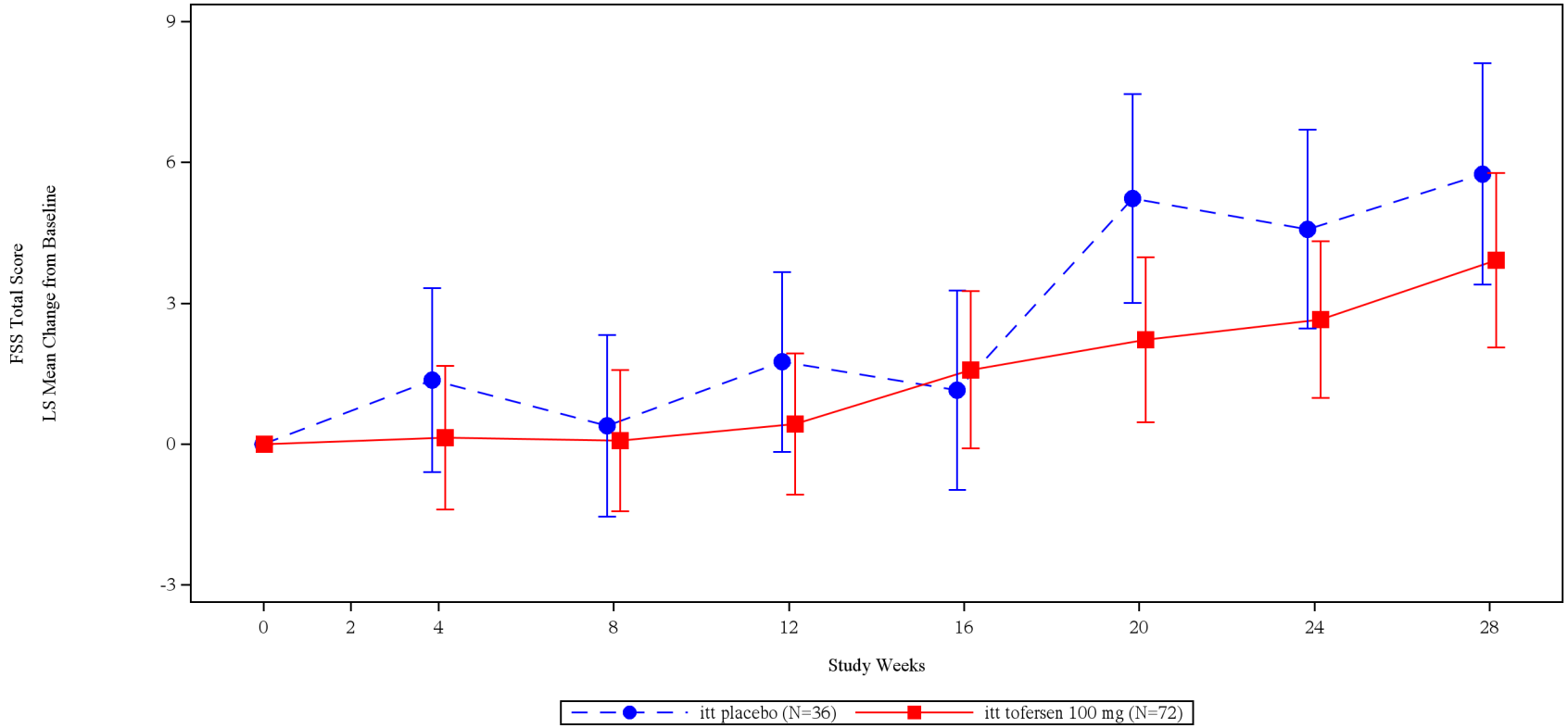

itt placebo n=	36	35	33	35	34	34	33	31
itt tofersen 100 mg n=	72	72	70	66	66	65	65	61

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-fss-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Line plot of FSS total score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 2: A negative change indicates less fatigue in everyday life.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-exp-fss-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in FSS total score > = 15%	40.4	34.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.88
SE of log(RR)		0.276
95% CI		(0.512, 1.513)
p-value		0.6437
Adjusted OR - Odds Ratio (tofersen/placebo)		0.81
SE of log(OR)		0.441
95% CI		(0.343, 1.931)
p-value		0.6414
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.103
95% CI		(-0.259, 0.147)
p-value		0.5877

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JUN2023

233AS101 Part C: Summary of proportion of improvement in FSS total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in FSS total score > = 15%	11.5	12.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.02
SE of log(RR)		0.592
95% CI		(0.319, 3.241)
p-value		0.9783
Adjusted OR - Odds Ratio (tofersen/placebo)		1.02
SE of log(OR)		0.616
95% CI		(0.304, 3.402)
p-value		0.9786
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.067
95% CI		(-0.125, 0.139)
p-value		0.9163

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-propim-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 15JUN2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	0.6	1.1
SE	1.94	1.51
95% CI	(-3.20, 4.41)	(-1.88, 4.04)
LS mean difference (tofersen - placebo)		0.5
SE		2.11
95% CI		(-3.66, 4.61)
p-value		0.8208
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.40, 0.40)
p-value		0.9987

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	34 (94.4)	70 (97.2)
Number of imputed values per imputation	2 (5.6)	2 (2.8)
LS mean change from baseline	3.2	1.8
SE	2.17	1.68
95% CI	(-1.08, 7.43)	(-1.52, 5.07)
LS mean difference (tofersen - placebo)		-1.4
SE		2.36
95% CI		(-6.02, 3.21)
p-value		0.5512
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.57, 0.25)
p-value		0.4439

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	5.8	2.4
SE	2.05	1.62
95% CI	(1.82, 9.85)	(-0.81, 5.54)
LS mean difference (tofersen - placebo)		-3.5
SE		2.24
95% CI		(-7.85, 0.91)
p-value		0.1205
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.76, 0.06)
p-value		0.0961

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	6.0	4.7
SE	2.28	1.78
95% CI	(1.51, 10.45)	(1.19, 8.15)
LS mean difference (tofersen - placebo)		-1.3
SE		2.49
95% CI		(-6.19, 3.57)
p-value		0.5993
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.51, 0.32)
p-value		0.6443

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	8.8	5.9
SE	2.48	1.96
95% CI	(3.90, 13.64)	(2.02, 9.69)
LS mean difference (tofersen - placebo)		-2.9
SE		2.71
95% CI		(-8.22, 2.39)
p-value		0.2820
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.65, 0.18)
p-value		0.2612

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	33 (91.7)	65 (90.3)
Number of imputed values per imputation	3 (8.3)	7 (9.7)
LS mean change from baseline	12.1	4.7
SE	2.69	2.10
95% CI	(6.82, 17.37)	(0.56, 8.80)
LS mean difference (tofersen - placebo)		-7.4
SE		2.93
95% CI		(-13.16, -1.68)
p-value		0.0113
Hedge's g standardized mean difference (tofersen - placebo)		-0.5
95% CI		(-0.95, -0.10)
p-value		0.0164

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	11.4	6.9
SE	3.10	2.43
95% CI	(5.29, 17.44)	(2.11, 11.65)
LS mean difference (tofersen - placebo)		-4.5
SE		3.38
95% CI		(-11.12, 2.14)
p-value		0.1848
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.75, 0.12)
p-value		0.1531

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

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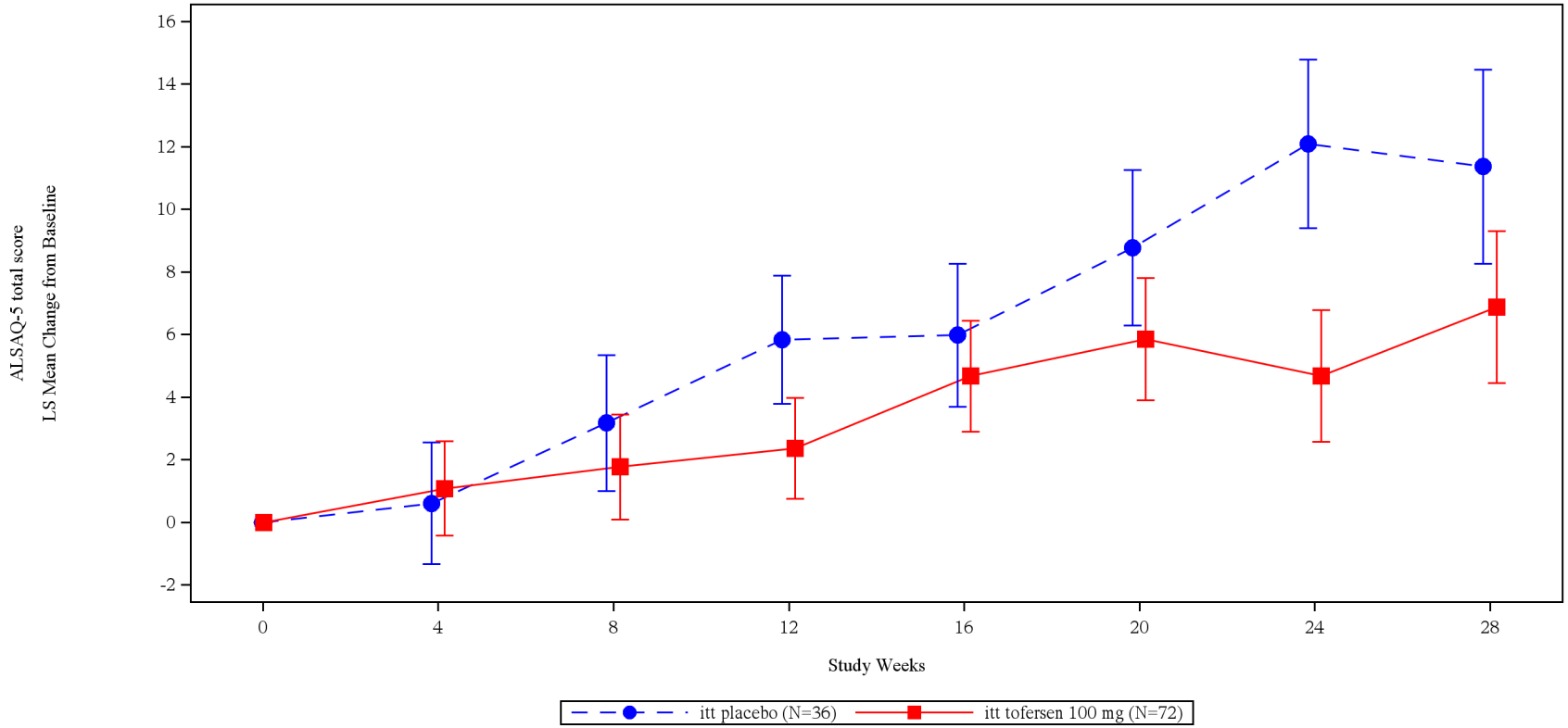

itt placebo n=	36	35	34	36	34	34	33	31
itt tofersen 100 mg n=	72	72	70	66	66	65	65	61

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-aq5-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 2: A negative change indicates better health-related status.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-exp-aq5-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JAN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	39.6	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.71
SE of log(RR)		0.294
95% CI		(0.397, 1.258)
p-value		0.2378
Adjusted OR - Odds Ratio (tofersen/placebo)		0.59
SE of log(OR)		0.451
95% CI		(0.245, 1.435)
p-value		0.2463
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.100
95% CI		(-0.318, 0.073)
p-value		0.2204

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 total score >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 total score > = 15%	6.1	6.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.97
SE of log(RR)		0.849
95% CI		(0.183, 5.109)
p-value		0.9695
Adjusted OR - Odds Ratio (tofersen/placebo)		0.97
SE of log(OR)		0.939
95% CI		(0.153, 6.089)
p-value		0.9707
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.051
95% CI		(-0.102, 0.100)
p-value		0.9827

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero total score at baseline are considered as worsening if their total scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

ALSA1-Difficult to Stand Up

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	57.5	36.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.65
SE of log(RR)		0.219
95% CI		(0.422, 0.994)
p-value		0.0470
Adjusted OR - Odds Ratio (tofersen/placebo)		0.44
SE of log(OR)		0.444
95% CI		(0.182, 1.039)
p-value		0.0611
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.21
SE of ARR		0.103
95% CI		(-0.412, -0.007)
p-value		0.0427

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

ALSA1-Difficulty Using My Arms and Hands

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	39.0	39.1
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.265
95% CI		(0.613, 1.730)
p-value		0.9124
Adjusted OR - Odds Ratio (tofersen/placebo)		1.05
SE of log(OR)		0.449
95% CI		(0.436, 2.535)
p-value		0.9116
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.103
95% CI		(-0.201, 0.203)
p-value		0.9925

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

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ALSA1-Difficulty Eating Solid Food

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	26.6	26.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.344
95% CI		(0.524, 2.016)
p-value		0.9364
Adjusted OR - Odds Ratio (tofersen/placebo)		1.04
SE of log(OR)		0.480
95% CI		(0.405, 2.661)
p-value		0.9376
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.093
95% CI		(-0.180, 0.183)
p-value		0.9892

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

ALSA1-My Speech Not Easy to Understand

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	20.7	21.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.06
SE of log(RR)		0.415
95% CI		(0.471, 2.400)
p-value		0.8825
Adjusted OR - Odds Ratio (tofersen/placebo)		1.08
SE of log(OR)		0.520
95% CI		(0.390, 2.991)
p-value		0.8824
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.086
95% CI		(-0.161, 0.178)
p-value		0.9232

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

ALSA1-Felt Hopeless About the Future

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	25.3	24.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.97
SE of log(RR)		0.383
95% CI		(0.460, 2.065)
p-value		0.9465
Adjusted OR - Odds Ratio (tofersen/placebo)		0.97
SE of log(OR)		0.486
95% CI		(0.374, 2.512)
p-value		0.9479
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.092
95% CI		(-0.189, 0.173)
p-value		0.9294

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 28.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

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ALSA1-Difficult to Stand Up

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.0	22.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.53
SE of log(RR)		0.484
95% CI		(0.592, 3.947)
p-value		0.3801
Adjusted OR - Odds Ratio (tofersen/placebo)		1.63
SE of log(OR)		0.551
95% CI		(0.554, 4.806)
p-value		0.3740
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.081
95% CI		(-0.080, 0.237)
p-value		0.3295

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

ALSA1-Difficulty Using My Arms and Hands

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.2	25.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.62
SE of log(RR)		0.460
95% CI		(0.657, 3.989)
p-value		0.2956
Adjusted OR - Odds Ratio (tofersen/placebo)		1.83
SE of log(OR)		0.563
95% CI		(0.609, 5.531)
p-value		0.2809
ARR - Absolute Risk Reduction (tofersen - placebo)		0.10
SE of ARR		0.082
95% CI		(-0.062, 0.258)
p-value		0.2287

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

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ALSA1-Difficulty Eating Solid Food

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	17.2	5.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.29
SE of log(RR)		0.706
95% CI		(0.074, 1.173)
p-value		0.0830
Adjusted OR - Odds Ratio (tofersen/placebo)		0.24
SE of log(OR)		0.806
95% CI		(0.050, 1.180)
p-value		0.0792
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.070
95% CI		(-0.256, 0.020)
p-value		0.0940

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

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ALSA1-My Speech Not Easy to Understand

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	2.8	1.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.62
SE of log(RR)		1.464
95% CI		(0.035, 10.931)
p-value		0.7442
Adjusted OR - Odds Ratio (tofersen/placebo)		0.62
SE of log(OR)		1.457
95% CI		(0.036, 10.815)
p-value		0.7444
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.032
95% CI		(-0.073, 0.054)
p-value		0.7636

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI - ITT population

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ALSA1-Felt Hopeless About the Future

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	19.1	19.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.06
SE of log(RR)		0.424
95% CI		(0.464, 2.443)
p-value		0.8820
Adjusted OR - Odds Ratio (tofersen/placebo)		1.08
SE of log(OR)		0.549
95% CI		(0.369, 3.184)
p-value		0.8825
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.083
95% CI		(-0.155, 0.171)
p-value		0.9268

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

Physical Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-2.5	-3.2
SE	1.12	0.88
95% CI	(-4.69, -0.31)	(-4.98, -1.52)
LS mean difference (tofersen - placebo)		-0.8
SE		1.22
95% CI		(-3.14, 1.64)
p-value		0.5368
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.32)
p-value		0.6843

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

Physical Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	32 (88.9)	63 (87.5)
Number of imputed values per imputation	4 (11.1)	9 (12.5)
LS mean change from baseline	-3.6	-3.7
SE	1.27	0.99
95% CI	(-6.09, -1.13)	(-5.63, -1.76)
LS mean difference (tofersen - placebo)		-0.1
SE		1.38
95% CI		(-2.80, 2.62)
p-value		0.9494
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.39, 0.46)
p-value		0.8560

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

Physical Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	-4.6	-3.5
SE	1.38	1.07
95% CI	(-7.31, -1.90)	(-5.56, -1.35)
LS mean difference (tofersen - placebo)		1.2
SE		1.52
95% CI		(-1.82, 4.13)
p-value		0.4484
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.22, 0.64)
p-value		0.3451

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

Mental Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Day 85		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-3.4	1.1
SE	1.67	1.33
95% CI	(-6.64, -0.11)	(-1.51, 3.70)
LS mean difference (tofersen - placebo)		4.5
SE		1.82
95% CI		(0.90, 8.04)
p-value		0.0140
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(0.03, 0.85)
p-value		0.0364

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

Mental Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	32 (88.9)	63 (87.5)
Number of imputed values per imputation	4 (11.1)	9 (12.5)
LS mean change from baseline	-4.9	-0.2
SE	1.85	1.44
95% CI	(-8.50, -1.26)	(-3.03, 2.62)
LS mean difference (tofersen - placebo)		4.7
SE		2.03
95% CI		(0.69, 8.67)
p-value		0.0215
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(0.00, 0.86)
p-value		0.0508

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: SF-36 component summary change from baseline by visit ANCOVA analysis using MI - ITT population

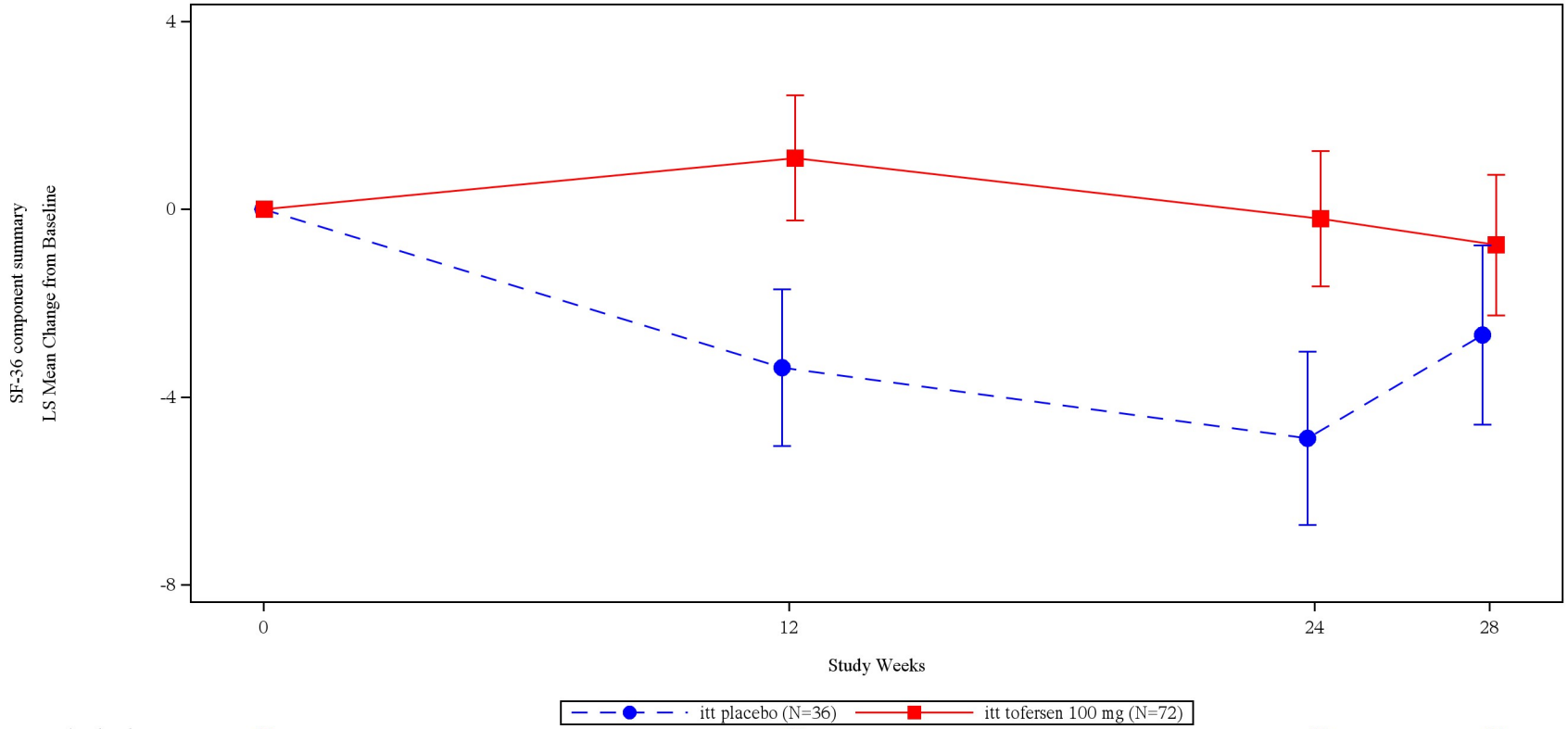
Mental Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	-2.7	-0.8
SE	1.91	1.50
95% CI	(-6.41, 1.06)	(-3.70, 2.19)
LS mean difference (tofersen - placebo)		1.9
SE		2.11
95% CI		(-2.23, 6.06)
p-value		0.3644
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.25, 0.61)
p-value		0.4147

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 24MAR2023

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

Mental Component Summary



itt placebo n=	36	36	32	31
itt tofersen 100 mg n=	72	67	63	61

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-sf36-anc-mi-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 25JAN2023

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

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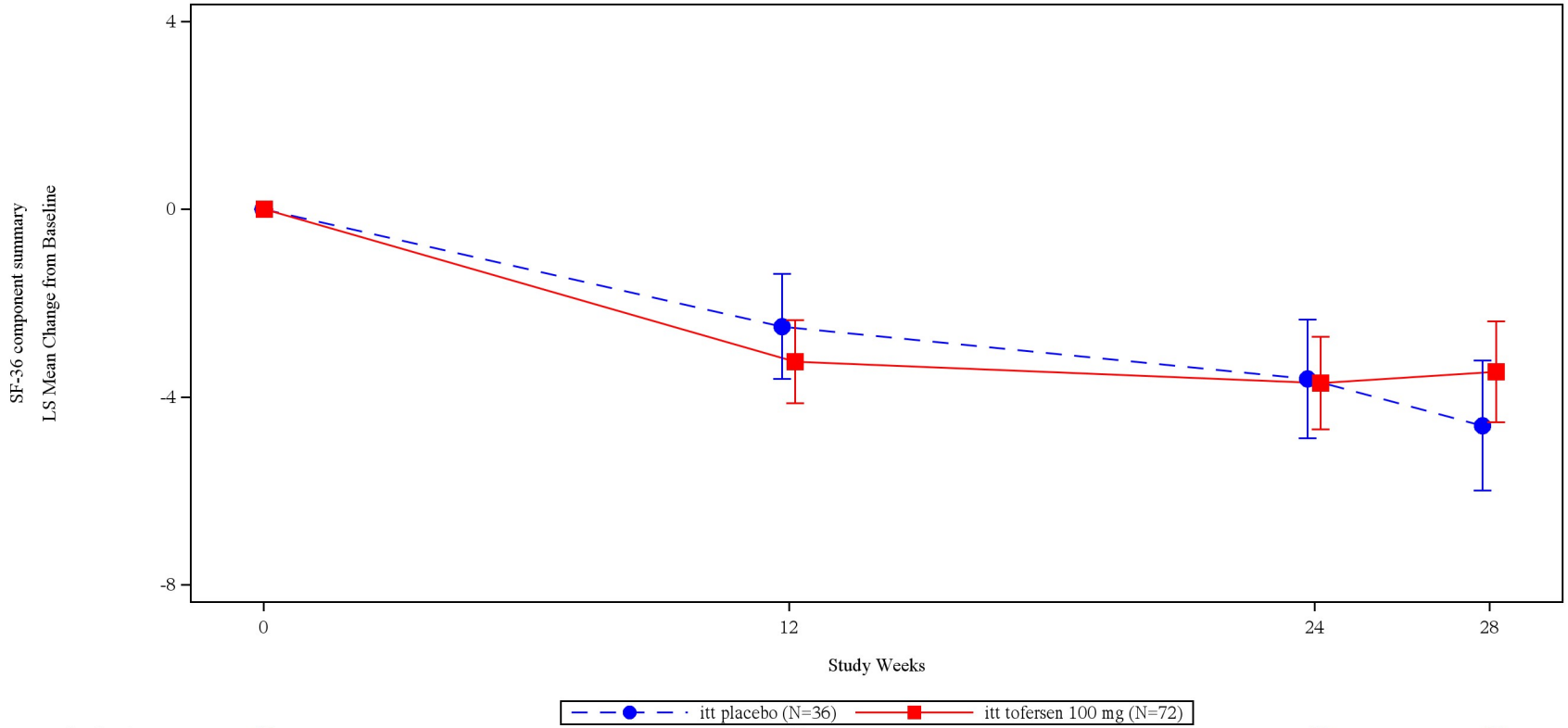
Physical Component Summary



itt placebo n=	36	36	32	31
itt tofersen 100 mg n=	72	67	63	61

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-sf36-anc-mi-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 25JAN2023

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-exp-sf36-anc-mi-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 25JAN2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI - ITT population

Mental Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	22.6	16.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.449
95% CI		(0.301, 1.750)
p-value		0.4752
Adjusted OR - Odds Ratio (tofersen/placebo)		0.68
SE of log(OR)		0.538
95% CI		(0.237, 1.953)
p-value		0.4738
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.087
95% CI		(-0.234, 0.105)
p-value		0.4548

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI - ITT population

Physical Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in SF-36 PCS > = 9.4	27.3	19.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.75
SE of log(RR)		0.360
95% CI		(0.372, 1.526)
p-value		0.4309
Adjusted OR - Odds Ratio (tofersen/placebo)		0.67
SE of log(OR)		0.522
95% CI		(0.240, 1.859)
p-value		0.4402
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.091
95% CI		(-0.257, 0.099)
p-value		0.3842

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06MAR2023

233AS101 Part C: Summary of proportion of improvement in SF-36 component summary at Week 28 using MI - ITT population

Mental Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in SF-36 MCS >= 9.6	10.4	13.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.35
SE of log(RR)		0.612
95% CI		(0.406, 4.463)
p-value		0.6279
Adjusted OR - Odds Ratio (tofersen/placebo)		1.40
SE of log(OR)		0.684
95% CI		(0.365, 5.344)
p-value		0.6254
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.069
95% CI		(-0.101, 0.169)
p-value		0.6245

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 02MAY2023

233AS101 Part C: Summary of proportion of improvement in SF-36 component summary at Week 28 using MI - ITT population

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Physical Component Summary

	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in SF-36 PCS >= 9.4	5.9	3.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.54
SE of log(RR)		0.948
95% CI		(0.084, 3.464)
p-value		0.5161
Adjusted OR - Odds Ratio (tofersen/placebo)		0.52
SE of log(OR)		1.027
95% CI		(0.069, 3.876)
p-value		0.5213
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.045
95% CI		(-0.116, 0.062)
p-value		0.5510

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 02MAY2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	71 (98.6)
Number of imputed values per imputation	0	1 (1.4)
Day 29		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	0.3
SE	0.43	0.34
95% CI	(-0.94, 0.73)	(-0.33, 0.99)
LS mean difference (tofersen - placebo)		0.4
SE		0.46
95% CI		(-0.47, 1.35)
p-value		0.3470
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.33, 0.48)
p-value		0.7052

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57		
Number of observations per imputation	33 (91.7)	70 (97.2)
Number of imputed values per imputation	3 (8.3)	2 (2.8)
LS mean change from baseline	0.6	0.6
SE	0.43	0.33
95% CI	(-0.28, 1.39)	(-0.09, 1.22)
LS mean difference (tofersen - placebo)		0.0
SE		0.46
95% CI		(-0.90, 0.92)
p-value		0.9794
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.31)
p-value		0.6195

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85		
Number of observations per imputation	35 (97.2)	66 (91.7)
Number of imputed values per imputation	1 (2.8)	6 (8.3)
LS mean change from baseline	0.4	0.6
SE	0.39	0.31
95% CI	(-0.32, 1.20)	(0.01, 1.20)
LS mean difference (tofersen - placebo)		0.2
SE		0.42
95% CI		(-0.66, 1.00)
p-value		0.6929
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.43, 0.39)
p-value		0.9230

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113		
Number of observations per imputation	34 (94.4)	66 (91.7)
Number of imputed values per imputation	2 (5.6)	6 (8.3)
LS mean change from baseline	0.5	0.6
SE	0.42	0.33
95% CI	(-0.33, 1.31)	(-0.06, 1.24)
LS mean difference (tofersen - placebo)		0.1
SE		0.46
95% CI		(-0.79, 1.00)
p-value		0.8210
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.48, 0.35)
p-value		0.7567

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141		
Number of observations per imputation	34 (94.4)	65 (90.3)
Number of imputed values per imputation	2 (5.6)	7 (9.7)
LS mean change from baseline	0.7	0.7
SE	0.40	0.32
95% CI	(-0.06, 1.52)	(0.10, 1.35)
LS mean difference (tofersen - placebo)		0.0
SE		0.44
95% CI		(-0.87, 0.87)
p-value		0.9950
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.31)
p-value		0.6204

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169		
Number of observations per imputation	33 (91.7)	64 (88.9)
Number of imputed values per imputation	3 (8.3)	8 (11.1)
LS mean change from baseline	0.9	0.5
SE	0.43	0.34
95% CI	(0.01, 1.70)	(-0.16, 1.18)
LS mean difference (tofersen - placebo)		-0.3
SE		0.48
95% CI		(-1.28, 0.58)
p-value		0.4631
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.66, 0.18)
p-value		0.2603

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: WPAI-Q6 change from baseline by visit ANCOVA analysis using MI - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
Number of observations per imputation	30 (83.3)	60 (83.3)
Number of imputed values per imputation	6 (16.7)	12 (16.7)
LS mean change from baseline	0.6	0.8
SE	0.42	0.34
95% CI	(-0.27, 1.40)	(0.13, 1.45)
LS mean difference (tofersen - placebo)		0.2
SE		0.47
95% CI		(-0.69, 1.14)
p-value		0.6286
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.46, 0.42)
p-value		0.9181

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 17MAR2023

233AS101 Part C: Line plot of WPAI-Q6 LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

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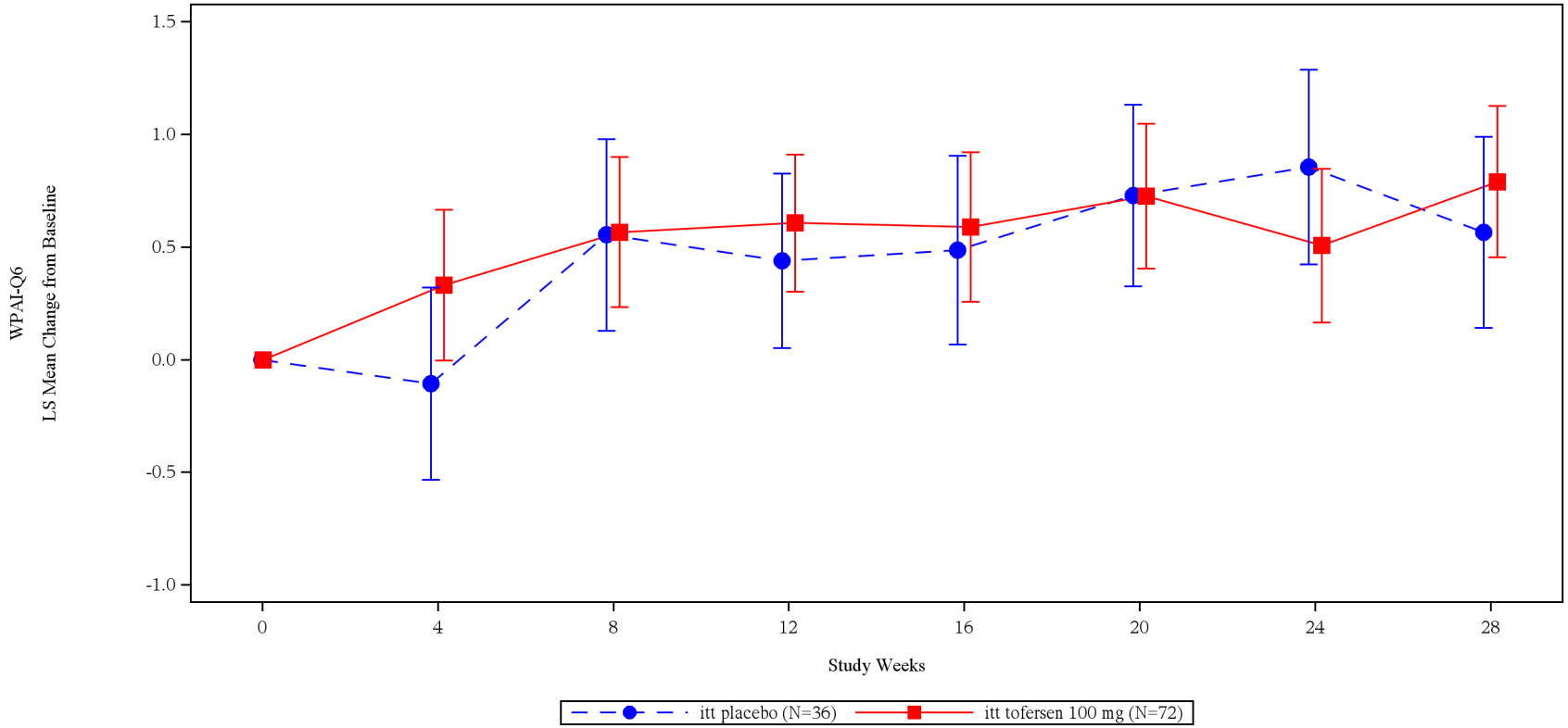

itt placebo n=	36	35	33	35	34	34	33	30
itt tofersen 100 mg n=	71	72	70	66	66	65	64	60

Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-exp-wpai-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 02FEB2023

233AS101 Part C: Line plot of WPAI-Q6 LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 2: A negative change indicates less activity impairment.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
NOTE 4: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-exp-wpai-anc-mi-chg-c.sas **Data Cutoff:** 16JUL2021 **Run Date:** 02FEB2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	31.8	31.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.02
SE of log(RR)		0.315
95% CI		(0.551, 1.896)
p-value		0.9439
Adjusted OR - Odds Ratio (tofersen/placebo)		1.03
SE of log(OR)		0.464
95% CI		(0.416, 2.564)
p-value		0.9447
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.099
95% CI		(-0.194, 0.196)
p-value		0.9944

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of improvement in WPAI-Q6 >= 15% at Week 28 using MI - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Average proportion of subjects with improvement in WPAI-Q6 score > = 15%	12.0	13.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.12
SE of log(RR)		0.582
95% CI		(0.359, 3.510)
p-value		0.8430
Adjusted OR - Odds Ratio (tofersen/placebo)		1.14
SE of log(OR)		0.662
95% CI		(0.312, 4.169)
p-value		0.8434
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.072
95% CI		(-0.124, 0.159)
p-value		0.8086

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propim-byvis-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15JUN2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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Suicidal Ideation (1-5)

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	2 (5.6)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.811
95% CI		(0.255, 6.131)
p-value		0.7833
OR - Odds Ratio (tofersen/placebo)		1.27
SE of log (OR)		0.863
95% CI		(0.234, 6.882)
p-value		0.7827
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.049
95% CI		(-0.081, 0.109)
p-value		0.7747

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(1) Wish to be dead

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	1 (2.8)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		2.00
SE of log (RR)		1.099
95% CI		(0.232, 17.247)
p-value		0.5283
OR - Odds Ratio (tofersen/placebo)		2.06
SE of log (OR)		1.137
95% CI		(0.222, 19.126)
p-value		0.5254
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.038
95% CI		(-0.048, 0.103)
p-value		0.4701

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(2) Non-specific active suicidal thoughts

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	2 (5.6)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.979
95% CI		(0.073, 3.406)
p-value		0.4789
OR - Odds Ratio (tofersen/placebo)		0.49
SE of log (OR)		1.022
95% CI		(0.066, 3.597)
p-value		0.4797
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.043
95% CI		(-0.112, 0.056)
p-value		0.5164

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.52
SE of log (RR)		1.620
95% CI		(0.063, 36.421)
p-value		0.7959
OR - Odds Ratio (tofersen/placebo)		1.53
SE of log (OR)		1.646
95% CI		(0.061, 38.535)
p-value		0.7956
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.025
95% CI		(-0.042, 0.056)
p-value		0.7803

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(4) Active suicidal ideation with some intent to act, without specific plan

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(5) Active suicidal ideation with specific plan and intent

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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Suicidal Behavior (6-11)

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(6) Preparatory acts or behavior

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(7) Aborted attempt

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(8) Interrupted attempt

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(9) Actual attempt

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(10) Suicidal behavior

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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(11) Suicide

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) - ITT population

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Self-injurious behavior without suicidal intent

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20MAR2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 1: Post-dose		
n	34	68
LS mean change from baseline	0.14	0.10
SE	0.182	0.139
95% CI	(-0.216, 0.506)	(-0.174, 0.379)
LS mean difference (tofersen - placebo)		-0.04
SE		0.191
95% CI		(-0.421, 0.336)
p-value		0.8251
Hedge's g standardized mean difference (tofersen - placebo)		-0.06
95% CI		(-0.474, 0.350)
p-value		0.7671

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 15: Pre-dose		
n	23	52
LS mean change from baseline	0.37	-0.20
SE	0.261	0.185
95% CI	(-0.155, 0.888)	(-0.567, 0.171)
LS mean difference (tofersen - placebo)		-0.56
SE		0.284
95% CI		(-1.132, 0.003)
p-value		0.0510
Hedge's g standardized mean difference (tofersen - placebo)		-0.46
95% CI		(-0.955, 0.038)
p-value		0.0703

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 15: Post-dose		
n	23	51
LS mean change from baseline	0.65	0.08
SE	0.159	0.113
95% CI	(0.333, 0.966)	(-0.146, 0.306)
LS mean difference (tofersen - placebo)		-0.57
SE		0.173
95% CI		(-0.915, -0.223)
p-value		0.0016
Hedge's g standardized mean difference (tofersen - placebo)		-0.59
95% CI		(-1.090, -0.087)
p-value		0.0215

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29: Pre-dose		
n	21	51
LS mean change from baseline	0.32	0.04
SE	0.267	0.183
95% CI	(-0.208, 0.858)	(-0.320, 0.410)
LS mean difference (tofersen - placebo)		-0.28
SE		0.291
95% CI		(-0.862, 0.302)
p-value		0.3398
Hedge's g standardized mean difference (tofersen - placebo)		-0.26
95% CI		(-0.767, 0.253)
p-value		0.3238

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 29: Post-dose		
n	22	49
LS mean change from baseline	0.56	0.22
SE	0.168	0.119
95% CI	(0.222, 0.893)	(-0.018, 0.456)
LS mean difference (tofersen - placebo)		-0.34
SE		0.185
95% CI		(-0.707, 0.030)
p-value		0.0709
Hedge's g standardized mean difference (tofersen - placebo)		-0.37
95% CI		(-0.879, 0.135)
p-value		0.1506

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57: Pre-dose		
n	21	46
LS mean change from baseline	0.57	0.16
SE	0.134	0.095
95% CI	(0.302, 0.837)	(-0.034, 0.346)
LS mean difference (tofersen - placebo)		-0.41
SE		0.148
95% CI		(-0.710, -0.117)
p-value		0.0071
Hedge's g standardized mean difference (tofersen - placebo)		-0.43
95% CI		(-0.952, 0.091)
p-value		0.1056

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 57: Post-dose		
n	21	46
LS mean change from baseline	0.45	0.10
SE	0.204	0.145
95% CI	(0.039, 0.854)	(-0.187, 0.392)
LS mean difference (tofersen - placebo)		-0.34
SE		0.226
95% CI		(-0.797, 0.108)
p-value		0.1330
Hedge's g standardized mean difference (tofersen - placebo)		-0.33
95% CI		(-0.852, 0.187)
p-value		0.2100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

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	placebo (N=36)	tofersen 100 mg (N=72)
Day 85: Pre-dose		
n	33	64
LS mean change from baseline	0.16	0.10
SE	0.188	0.144
95% CI	(-0.209, 0.537)	(-0.189, 0.383)
LS mean difference (tofersen - placebo)		-0.07
SE		0.199
95% CI		(-0.462, 0.327)
p-value		0.7354
Hedge's g standardized mean difference (tofersen - placebo)		-0.05
95% CI		(-0.468, 0.373)
p-value		0.8247

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 85: Post-dose		
n	35	62
LS mean change from baseline	0.38	0.09
SE	0.198	0.156
95% CI	(-0.010, 0.778)	(-0.224, 0.395)
LS mean difference (tofersen - placebo)		-0.30
SE		0.211
95% CI		(-0.718, 0.122)
p-value		0.1621
Hedge's g standardized mean difference (tofersen - placebo)		-0.28
95% CI		(-0.700, 0.133)
p-value		0.1824

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113: Pre-dose		
n	18	43
LS mean change from baseline	0.60	0.08
SE	0.256	0.172
95% CI	(0.083, 1.111)	(-0.260, 0.430)
LS mean difference (tofersen - placebo)		-0.51
SE		0.287
95% CI		(-1.087, 0.062)
p-value		0.0794
Hedge's g standardized mean difference (tofersen - placebo)		-0.44
95% CI		(-0.991, 0.121)
p-value		0.1253

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 113: Post-dose		
n	17	43
LS mean change from baseline	0.53	0.19
SE	0.221	0.145
95% CI	(0.084, 0.971)	(-0.097, 0.485)
LS mean difference (tofersen - placebo)		-0.33
SE		0.247
95% CI		(-0.828, 0.161)
p-value		0.1820
Hedge's g standardized mean difference (tofersen - placebo)		-0.31
95% CI		(-0.870, 0.259)
p-value		0.2884

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141: Pre-dose		
n	16	38
LS mean change from baseline	0.15	0.19
SE	0.291	0.193
95% CI	(-0.438, 0.734)	(-0.196, 0.579)
LS mean difference (tofersen - placebo)		0.04
SE		0.328
95% CI		(-0.616, 0.702)
p-value		0.8952
Hedge's g standardized mean difference (tofersen - placebo)		-0.04
95% CI		(-0.619, 0.549)
p-value		0.9062

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
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Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 141: Post-dose		
n	15	38
LS mean change from baseline	0.42	0.23
SE	0.249	0.160
95% CI	(-0.077, 0.924)	(-0.095, 0.549)
LS mean difference (tofersen - placebo)		-0.20
SE		0.280
95% CI		(-0.759, 0.366)
p-value		0.4859
Hedge's g standardized mean difference (tofersen - placebo)		-0.26
95% CI		(-0.859, 0.340)
p-value		0.3961

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169: Pre-dose		
n	33	64
LS mean change from baseline	0.06	-0.02
SE	0.219	0.172
95% CI	(-0.372, 0.498)	(-0.358, 0.327)
LS mean difference (tofersen - placebo)		-0.08
SE		0.242
95% CI		(-0.559, 0.403)
p-value		0.7486
Hedge's g standardized mean difference (tofersen - placebo)		0.01
95% CI		(-0.411, 0.429)
p-value		0.9680

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 169: Post-dose		
n	31	62
LS mean change from baseline	0.06	0.13
SE	0.209	0.162
95% CI	(-0.353, 0.477)	(-0.188, 0.457)
LS mean difference (tofersen - placebo)		0.07
SE		0.232
95% CI		(-0.388, 0.533)
p-value		0.7551
Hedge's g standardized mean difference (tofersen - placebo)		0.14
95% CI		(-0.290, 0.573)
p-value		0.5206

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
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NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline by visit ANCOVA analysis (observed data) - ITT population

	placebo (N=36)	tofersen 100 mg (N=72)
Day 197		
n	30	58
LS mean change from baseline	0.10	0.11
SE	0.243	0.189
95% CI	(-0.387, 0.580)	(-0.262, 0.491)
LS mean difference (tofersen - placebo)		0.02
SE		0.272
95% CI		(-0.523, 0.559)
p-value		0.9465
Hedge's g standardized mean difference (tofersen - placebo)		0.01
95% CI		(-0.430, 0.452)
p-value		0.9601

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: Number of subjects with at least one adverse event - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	34 (94.4)	69 (95.8)
RR - Relative Risk (tofersen/placebo)		1.01
SE of log (RR)		0.047
95% CI		(0.925, 1.113)
p-value		0.7576
OR - Odds Ratio (tofersen/placebo)		1.35
SE of log (OR)		0.937
95% CI		(0.216, 8.482)
p-value		0.7469
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.045
95% CI		(-0.074, 0.102)
p-value		0.7568

Source: biib067/valueaccess/amnog/t-ae-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 20JAN2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Injury, poisoning and procedural complications

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	29 (80.6)	49 (68.1)
RR - Relative Risk (tofersen/placebo)		0.84
SE of log (RR)		0.115
95% CI		(0.674, 1.058)
p-value		0.1426
OR - Odds Ratio (tofersen/placebo)		0.51
SE of log (OR)		0.491
95% CI		(0.196, 1.347)
p-value		0.1757
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.086
95% CI		(-0.293, 0.043)
p-value		0.1454

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

Nervous system disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	22 (61.1)	47 (65.3)
RR - Relative Risk (tofersen/placebo)		1.07
SE of log (RR)		0.158
95% CI		(0.783, 1.457)
p-value		0.6770
OR - Odds Ratio (tofersen/placebo)		1.20
SE of log (OR)		0.422
95% CI		(0.523, 2.736)
p-value		0.6710
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.099
95% CI		(-0.152, 0.235)
p-value		0.6730

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Musculoskeletal and connective tissue disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	18 (50.0)	40 (55.6)
RR - Relative Risk (tofersen/placebo)		1.11
SE of log (RR)		0.197
95% CI		(0.755, 1.635)
p-value		0.5932
OR - Odds Ratio (tofersen/placebo)		1.25
SE of log (OR)		0.409
95% CI		(0.561, 2.787)
p-value		0.5854
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.102
95% CI		(-0.144, 0.255)
p-value		0.5854

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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General disorders and administration site conditions

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	9 (25.0)	24 (33.3)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.333
95% CI		(0.694, 2.563)
p-value		0.3881
OR - Odds Ratio (tofersen/placebo)		1.50
SE of log (OR)		0.459
95% CI		(0.610, 3.688)
p-value		0.3770
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.091
95% CI		(-0.095, 0.262)
p-value		0.3602

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Gastrointestinal disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	16 (44.4)	22 (30.6)
RR - Relative Risk (tofersen/placebo)		0.69
SE of log (RR)		0.257
95% CI		(0.415, 1.139)
p-value		0.1456
OR - Odds Ratio (tofersen/placebo)		0.55
SE of log (OR)		0.422
95% CI		(0.241, 1.257)
p-value		0.1564
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.14
SE of ARR		0.099
95% CI		(-0.333, 0.055)
p-value		0.1607

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	13 (36.1)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		0.69
SE of log (RR)		0.301
95% CI		(0.384, 1.250)
p-value		0.2224
OR - Odds Ratio (tofersen/placebo)		0.59
SE of log (OR)		0.441
95% CI		(0.248, 1.400)
p-value		0.2311
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.095
95% CI		(-0.297, 0.075)
p-value		0.2418

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Infections and infestations

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	15 (41.7)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.303
95% CI		(0.276, 0.905)
p-value		0.0221
OR - Odds Ratio (tofersen/placebo)		0.37
SE of log (OR)		0.446
95% CI		(0.154, 0.882)
p-value		0.0250
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.21
SE of ARR		0.095
95% CI		(-0.395, -0.022)
p-value		0.0285

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Investigations

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	3 (8.3)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		0.599
95% CI		(0.773, 8.081)
p-value		0.1258
OR - Odds Ratio (tofersen/placebo)		2.89
SE of log (OR)		0.669
95% CI		(0.780, 10.746)
p-value		0.1122
ARR - Absolute Risk Reduction (tofersen/placebo)		0.13
SE of ARR		0.066
95% CI		(-0.005, 0.255)
p-value		0.0599

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Skin and subcutaneous tissue disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	3 (8.3)	11 (15.3)
RR - Relative Risk (tofersen/placebo)		1.83
SE of log (RR)		0.619
95% CI		(0.545, 6.162)
p-value		0.3271
OR - Odds Ratio (tofersen/placebo)		1.98
SE of log (OR)		0.686
95% CI		(0.517, 7.614)
p-value		0.3183
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.063
95% CI		(-0.053, 0.192)
p-value		0.2673

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

Psychiatric disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	6 (16.7)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.486
95% CI		(0.289, 1.944)
p-value		0.5538
OR - Odds Ratio (tofersen/placebo)		0.71
SE of log (OR)		0.572
95% CI		(0.233, 2.191)
p-value		0.5563
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.073
95% CI		(-0.185, 0.102)
p-value		0.5699

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class - safety population

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Metabolism and nutrition disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	5 (13.9)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.60
SE of log (RR)		0.570
95% CI		(0.196, 1.834)
p-value		0.3702
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.643
95% CI		(0.160, 1.989)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.066
95% CI		(-0.185, 0.074)
p-value		0.4014

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Procedural pain

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	21 (58.3)	41 (56.9)
RR - Relative Risk (tofersen/placebo)		0.98
SE of log (RR)		0.174
95% CI		(0.694, 1.373)
p-value		0.8900
OR - Odds Ratio (tofersen/placebo)		0.94
SE of log (OR)		0.413
95% CI		(0.420, 2.124)
p-value		0.8906
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.101
95% CI		(-0.211, 0.184)
p-value		0.8904

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Headache

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	16 (44.4)	33 (45.8)
RR - Relative Risk (tofersen/placebo)		1.03
SE of log (RR)		0.226
95% CI		(0.662, 1.606)
p-value		0.8918
OR - Odds Ratio (tofersen/placebo)		1.06
SE of log (OR)		0.410
95% CI		(0.473, 2.364)
p-value		0.8913
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.102
95% CI		(-0.185, 0.213)
p-value		0.8912

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Pain in extremity

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	6 (16.7)	19 (26.4)
RR - Relative Risk (tofersen/placebo)		1.58
SE of log (RR)		0.421
95% CI		(0.693, 3.617)
p-value		0.2756
OR - Odds Ratio (tofersen/placebo)		1.79
SE of log (OR)		0.521
95% CI		(0.646, 4.977)
p-value		0.2627
ARR - Absolute Risk Reduction (tofersen/placebo)		0.10
SE of ARR		0.081
95% CI		(-0.061, 0.256)
p-value		0.2299

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

Injury, poisoning and procedural complications/Fall

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	15 (41.7)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		0.57
SE of log (RR)		0.290
95% CI		(0.321, 0.999)
p-value		0.0498
OR - Odds Ratio (tofersen/placebo)		0.43
SE of log (OR)		0.437
95% CI		(0.184, 1.020)
p-value		0.0555
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.18
SE of ARR		0.096
95% CI		(-0.369, 0.008)
p-value		0.0606

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Back pain

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	2 (5.6)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		3.75
SE of log (RR)		0.725
95% CI		(0.906, 15.516)
p-value		0.0681
OR - Odds Ratio (tofersen/placebo)		4.47
SE of log (OR)		0.783
95% CI		(0.964, 20.770)
p-value		0.0558
ARR - Absolute Risk Reduction (tofersen/placebo)		0.15
SE of ARR		0.061
95% CI		(0.033, 0.273)
p-value		0.0126

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post lumbar puncture syndrome

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	11 (30.6)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.59
SE of log (RR)		0.355
95% CI		(0.295, 1.185)
p-value		0.1386
OR - Odds Ratio (tofersen/placebo)		0.50
SE of log (OR)		0.474
95% CI		(0.198, 1.268)
p-value		0.1446
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.089
95% CI		(-0.300, 0.050)
p-value		0.1609

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Fatigue

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	2 (5.6)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		3.00
SE of log (RR)		0.736
95% CI		(0.709, 12.694)
p-value		0.1355
OR - Odds Ratio (tofersen/placebo)		3.40
SE of log (OR)		0.793
95% CI		(0.718, 16.098)
p-value		0.1229
ARR - Absolute Risk Reduction (tofersen/placebo)		0.11
SE of ARR		0.058
95% CI		(-0.003, 0.225)
p-value		0.0562

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

Musculoskeletal and connective tissue disorders/Arthralgia

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	2 (5.6)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		0.747
95% CI		(0.578, 10.814)
p-value		0.2201
OR - Odds Ratio (tofersen/placebo)		2.74
SE of log (OR)		0.803
95% CI		(0.568, 13.242)
p-value		0.2093
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.056
95% CI		(-0.026, 0.193)
p-value		0.1356

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Myalgia

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	2 (5.6)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		0.747
95% CI		(0.578, 10.814)
p-value		0.2201
OR - Odds Ratio (tofersen/placebo)		2.74
SE of log (OR)		0.803
95% CI		(0.568, 13.242)
p-value		0.2093
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.056
95% CI		(-0.026, 0.193)
p-value		0.1356

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Nausea

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	6 (16.7)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.486
95% CI		(0.289, 1.944)
p-value		0.5538
OR - Odds Ratio (tofersen/placebo)		0.71
SE of log (OR)		0.572
95% CI		(0.233, 2.191)
p-value		0.5563
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.073
95% CI		(-0.185, 0.102)
p-value		0.5699

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Constipation

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.612
95% CI		(0.226, 2.491)
p-value		0.6385
OR - Odds Ratio (tofersen/placebo)		0.73
SE of log (OR)		0.680
95% CI		(0.192, 2.760)
p-value		0.6398
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.062
95% CI		(-0.149, 0.093)
p-value		0.6525

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

Nervous system disorders/Paraesthesia

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	6 (16.7)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.540
95% CI		(0.173, 1.441)
p-value		0.1993
OR - Odds Ratio (tofersen/placebo)		0.45
SE of log (OR)		0.618
95% CI		(0.135, 1.526)
p-value		0.2020
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.070
95% CI		(-0.221, 0.054)
p-value		0.2348

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Muscular weakness

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Neck pain

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Dyspnoea

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	5 (13.9)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.40
SE of log (RR)		0.639
95% CI		(0.114, 1.400)
p-value		0.1516
OR - Odds Ratio (tofersen/placebo)		0.36
SE of log (OR)		0.705
95% CI		(0.092, 1.452)
p-value		0.1525
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.064
95% CI		(-0.208, 0.041)
p-value		0.1904

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post procedural complication

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Nasopharyngitis

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	7 (19.4)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.14
SE of log (RR)		0.775
95% CI		(0.031, 0.653)
p-value		0.0121
OR - Odds Ratio (tofersen/placebo)		0.12
SE of log (OR)		0.832
95% CI		(0.023, 0.604)
p-value		0.0103
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.17
SE of ARR		0.069
95% CI		(-0.301, -0.032)
p-value		0.0153

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Diarrhoea

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	5 (13.9)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.10
SE of log (RR)		1.076
95% CI		(0.012, 0.824)
p-value		0.0324
OR - Odds Ratio (tofersen/placebo)		0.09
SE of log (OR)		1.116
95% CI		(0.010, 0.779)
p-value		0.0290
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.059
95% CI		(-0.241, -0.009)
p-value		0.0349

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with adverse event by maximum CTCAE grade - safety population

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with events at maximum CTCAE grade 1	15 (41.7)	25 (34.7)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.255
95% CI		(0.506, 1.374)
p-value		0.4745
OR - Odds Ratio (tofersen/placebo)		0.74
SE of log (OR)		0.419
95% CI		(0.328, 1.693)
p-value		0.4817
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.099
95% CI		(-0.264, 0.126)
p-value		0.4852

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 03FEB2023

233AS101 Part C: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with events at maximum CTCAE grade 2	15 (41.7)	32 (44.4)
RR - Relative Risk (tofersen/placebo)		1.07
SE of log (RR)		0.237
95% CI		(0.670, 1.698)
p-value		0.7855
OR - Odds Ratio (tofersen/placebo)		1.12
SE of log (OR)		0.413
95% CI		(0.499, 2.516)
p-value		0.7838
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.101
95% CI		(-0.170, 0.226)
p-value		0.7831

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 03FEB2023

233AS101 Part C: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with events at maximum CTCAE grade 3	4 (11.1)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.555
95% CI		(0.421, 3.712)
p-value		0.6878
OR - Odds Ratio (tofersen/placebo)		1.29
SE of log (OR)		0.630
95% CI		(0.375, 4.439)
p-value		0.6860
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.066
95% CI		(-0.102, 0.158)
p-value		0.6755

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 03FEB2023

233AS101 Part C: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with events at maximum CTCAE grade 4	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.52
SE of log (RR)		1.620
95% CI		(0.063, 36.421)
p-value		0.7959
OR - Odds Ratio (tofersen/placebo)		1.53
SE of log (OR)		1.646
95% CI		(0.061, 38.535)
p-value		0.7956
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.025
95% CI		(-0.042, 0.056)
p-value		0.7803

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 03FEB2023

233AS101 Part C: Number of subjects with adverse event by maximum CTCAE grade - safety population

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with events at maximum CTCAE grade 5	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.52
SE of log (RR)		1.620
95% CI		(0.063, 36.421)
p-value		0.7959
OR - Odds Ratio (tofersen/placebo)		1.53
SE of log (OR)		1.646
95% CI		(0.061, 38.535)
p-value		0.7956
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.025
95% CI		(-0.042, 0.056)
p-value		0.7803

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 03FEB2023

233AS101 Part C: Number of subjects with at least one serious adverse event - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any serious event	5 (13.9)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		1.30
SE of log (RR)		0.485
95% CI		(0.502, 3.364)
p-value		0.5886
OR - Odds Ratio (tofersen/placebo)		1.37
SE of log (OR)		0.571
95% CI		(0.446, 4.184)
p-value		0.5849
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.073
95% CI		(-0.102, 0.185)
p-value		0.5699

Source: biib067/valueaccess/amnog/t-sae-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23JAN2023

233AS101 Part C: Number of subjects with at least one serious adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		0.63
SE of log (RR)		0.639
95% CI		(0.179, 2.187)
p-value		0.4620
OR - Odds Ratio (tofersen/placebo)		0.60
SE of log (OR)		0.704
95% CI		(0.150, 2.374)
p-value		0.4640
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.060
95% CI		(-0.160, 0.077)
p-value		0.4899

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Dyspnoea

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		0.10
SE of log (RR)		1.536
95% CI		(0.005, 2.058)
p-value		0.1362
OR - Odds Ratio (tofersen/placebo)		0.10
SE of log (OR)		1.563
95% CI		(0.004, 2.037)
p-value		0.1324
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.042
95% CI		(-0.144, 0.022)
p-value		0.1519

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any grade >= 3 event	4 (11.1)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.540
95% CI		(0.520, 4.323)
p-value		0.4528
OR - Odds Ratio (tofersen/placebo)		1.60
SE of log (OR)		0.617
95% CI		(0.477, 5.367)
p-value		0.4465
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.068
95% CI		(-0.078, 0.190)
p-value		0.4164

Source: biib067/valueaccess/amnog/t-ae-ctc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23JAN2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Injury, poisoning and procedural complications

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include system organ class with >=5% patients with events in total population OR (at least 10 patients with events and >= 1% patients with events) in either treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

Respiratory, thoracic and mediastinal disorders

	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include system organ class with >=5% patients with events in total population OR (at least 10 patients with events and >= 1% patients with events) in either treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-soc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation - safety population

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	placebo (N=36)	tofersen 100 mg (N=72)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

Source: biib067/valueaccess/amnog/t-ae-disc-event.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23JAN2023

233AS101 Part C: Adverse events that led to withdrawal from study by system organ class and preferred term - safety population

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	placebo (N=36) n (%)	tofersen 100 mg (N=72) n (%)
Number of subjects with any event that led to withdrawal	0	3 (4.2)
Cardiac disorders	0	1 (1.4)
Cardiac failure congestive	0	1 (1.4)
Infections and infestations	0	1 (1.4)
Myelitis	0	1 (1.4)
Injury, poisoning and procedural complications	0	1 (1.4)
Meningitis chemical	0	1 (1.4)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 24.0).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/233as101-partc/csr/t-ae-wd-socpt.sas:t-ae-wd-socpt-all.rtf **Run Date:** 22SEP2021

233AS101 Part C: Adverse events that led to discontinuation of study drug by system organ class and preferred term - safety population

Page: 1 of 1

	placebo (N=36) n (%)	tofersen 100 mg (N=72) n (%)
Number of subjects with any event that led to discontinuation	[redacted]	
Cardiac disorders	0	1 (1.4)
Cardiac failure congestive	0	1 (1.4)
Infections and infestations	0	1 (1.4)
Myelitis	0	1 (1.4)
Injury, poisoning and procedural complications	0	1 (1.4)
Meningitis chemical	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	[redacted]	
Pulmonary embolism		

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 24.0).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/233as101-partc/csr/t-ae-disc-socpt.sas:t-ae-disc-socpt-all.rtf **Run Date:** 22SEP2021

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233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	37.7 (6.73)	35.2 (6.27)
Median	38.0	36.0
Q1, Q3	34.0, 41.0	34.0, 39.0
Min, Max	24, 47	15, 48
Gender - Male		
n	19	43
Mean (SD)	36.9 (5.01)	38.1 (5.40)
Median	38.0	40.0
Q1, Q3	33.0, 42.0	35.0, 42.0
Min, Max	25, 44	25, 46

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	36.1 (5.96)	37.7 (6.24)
Median	38.0	39.0
Q1, Q3	33.0, 40.0	35.0, 41.0
Min, Max	24, 45	15, 48
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	38.2 (5.68)	36.0 (5.46)
Median	39.0	37.0
Q1, Q3	34.0, 42.0	33.0, 40.0
Min, Max	25, 47	23, 45

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	39.6 (4.90)	37.5 (5.06)
Median	39.5	38.0
Q1, Q3	35.5, 43.5	35.0, 40.0
Min, Max	32, 47	25, 48
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	34.5 (5.76)	36.4 (6.60)
Median	35.5	38.0
Q1, Q3	32.5, 39.0	34.0, 41.0
Min, Max	24, 42	15, 46

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	36.5 (6.39)	36.5 (5.49)
Median	37.5	37.0
Q1, Q3	33.0, 41.0	34.0, 40.0
Min, Max	24, 46	23, 48
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	38.5 (4.74)	37.6 (6.59)
Median	38.5	40.0
Q1, Q3	34.0, 42.0	35.0, 42.0
Min, Max	32, 47	15, 46

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	35.4 (5.66)	36.0 (6.40)
Median	37.0	37.0
Q1, Q3	33.0, 39.0	33.0, 40.0
Min, Max	24, 45	15, 44
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	39.9 (5.09)	38.1 (5.13)
Median	40.0	39.0
Q1, Q3	35.0, 44.0	36.0, 41.0
Min, Max	32, 47	26, 48

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	38.3 (5.48)	38.1 (6.31)
Median	39.0	40.0
Q1, Q3	33.0, 42.0	36.0, 42.0
Min, Max	25, 47	15, 48
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	35.5 (6.17)	34.8 (4.49)
Median	36.0	35.0
Q1, Q3	33.0, 40.0	33.0, 37.0
Min, Max	24, 45	23, 41

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	10.6 (1.77)	10.8 (2.51)
Median	11.0	12.0
Q1, Q3	9.0, 12.0	11.0, 12.0
Min, Max	7, 12	1, 12
Gender - Male		
n	19	43
Mean (SD)	10.8 (1.87)	11.2 (1.57)
Median	11.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	5, 12	4, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	10.7 (1.44)	10.8 (2.43)
Median	11.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	7, 12	1, 12
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	10.7 (2.05)	11.3 (1.36)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	5, 12	6, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.

Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	11.3 (1.03)	11.4 (0.93)
Median	12.0	12.0
Q1, Q3	11.0, 12.0	11.0, 12.0
Min, Max	9, 12	8, 12
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	10.0 (2.28)	10.6 (2.56)
Median	11.0	12.0
Q1, Q3	8.0, 12.0	10.0, 12.0
Min, Max	5, 12	1, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	10.8 (1.77)	11.2 (1.65)
Median	11.5	12.0
Q1, Q3	11.0, 12.0	11.0, 12.0
Min, Max	7, 12	4, 12
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	10.6 (1.91)	10.7 (2.48)
Median	11.0	12.0
Q1, Q3	10.0, 12.0	10.0, 12.0
Min, Max	5, 12	1, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	10.4 (1.96)	10.6 (2.52)
Median	11.0	12.0
Q1, Q3	10.0, 12.0	10.0, 12.0
Min, Max	5, 12	1, 12
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	11.2 (1.47)	11.5 (0.94)
Median	12.0	12.0
Q1, Q3	11.0, 12.0	11.0, 12.0
Min, Max	7, 12	8, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Bulbar Function Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	11.1 (1.44)	11.2 (2.11)
Median	12.0	12.0
Q1, Q3	11.0, 12.0	11.0, 12.0
Min, Max	7, 12	1, 12
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	10.1 (2.22)	10.7 (1.78)
Median	11.0	11.5
Q1, Q3	9.0, 12.0	10.0, 12.0
Min, Max	5, 12	6, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	8.8 (2.44)	7.8 (2.35)
Median	9.0	8.0
Q1, Q3	7.0, 10.0	6.0, 10.0
Min, Max	4, 12	3, 12
Gender - Male		
n	19	43
Mean (SD)	8.2 (2.81)	8.4 (2.50)
Median	9.0	9.0
Q1, Q3	6.0, 10.0	7.0, 10.0
Min, Max	1, 12	0, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	8.1 (2.80)	8.4 (2.80)
Median	9.0	9.0
Q1, Q3	7.0, 10.0	7.0, 10.0
Min, Max	1, 12	0, 12
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	8.7 (2.54)	7.9 (1.97)
Median	9.0	8.0
Q1, Q3	6.0, 11.0	6.0, 9.0
Min, Max	4, 12	4, 11

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.

Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	9.0 (2.39)	8.1 (2.60)
Median	9.0	8.0
Q1, Q3	7.5, 11.0	6.0, 10.0
Min, Max	5, 12	0, 12
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	7.8 (2.83)	8.2 (2.32)
Median	9.0	9.0
Q1, Q3	6.0, 10.0	7.0, 10.0
Min, Max	1, 11	3, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	7.9 (2.91)	7.9 (2.54)
Median	8.5	8.0
Q1, Q3	6.0, 10.0	6.0, 10.0
Min, Max	1, 12	0, 12
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	9.3 (1.90)	8.6 (2.24)
Median	9.0	9.0
Q1, Q3	9.0, 11.0	8.0, 10.0
Min, Max	5, 12	3, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	7.9 (2.76)	7.8 (2.76)
Median	9.0	8.0
Q1, Q3	6.0, 10.0	6.0, 10.0
Min, Max	1, 12	0, 12
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	9.3 (2.25)	8.7 (1.93)
Median	9.0	9.0
Q1, Q3	8.0, 11.0	8.0, 10.0
Min, Max	5, 12	5, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	8.5 (2.33)	8.5 (2.55)
Median	9.0	9.0
Q1, Q3	6.0, 10.0	7.0, 10.0
Min, Max	4, 12	0, 12
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	8.3 (3.17)	7.5 (2.12)
Median	9.0	8.0
Q1, Q3	7.0, 11.0	6.0, 9.0
Min, Max	1, 12	3, 11

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	7.2 (2.92)	5.9 (1.92)
Median	7.0	6.0
Q1, Q3	6.0, 8.0	5.0, 6.0
Min, Max	2, 12	3, 12
Gender - Male		
n	19	43
Mean (SD)	7.3 (2.31)	7.4 (2.50)
Median	7.0	7.0
Q1, Q3	6.0, 8.0	6.0, 9.0
Min, Max	1, 11	1, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	6.5 (2.95)	7.5 (2.53)
Median	7.0	7.0
Q1, Q3	5.0, 8.0	6.0, 9.0
Min, Max	1, 12	1, 12
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	7.7 (2.22)	5.9 (1.94)
Median	7.0	6.0
Q1, Q3	6.0, 8.0	5.0, 7.0
Min, Max	5, 12	3, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.

Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	8.1 (2.27)	6.6 (2.50)
Median	7.5	6.0
Q1, Q3	6.5, 10.5	5.0, 8.0
Min, Max	5, 12	1, 12
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	6.1 (2.58)	6.9 (2.32)
Median	6.0	6.5
Q1, Q3	5.0, 8.0	5.0, 8.0
Min, Max	1, 11	3, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	6.8 (2.71)	6.3 (2.04)
Median	7.0	6.0
Q1, Q3	5.0, 8.0	5.0, 7.0
Min, Max	1, 12	1, 12
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	7.9 (2.27)	7.5 (2.76)
Median	7.5	8.0
Q1, Q3	6.0, 11.0	5.0, 10.0
Min, Max	5, 11	3, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	6.7 (2.73)	6.9 (2.41)
Median	7.0	6.0
Q1, Q3	5.0, 8.0	5.0, 8.0
Min, Max	1, 12	1, 12
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	8.0 (2.20)	6.7 (2.41)
Median	7.0	6.0
Q1, Q3	6.0, 11.0	5.0, 8.0
Min, Max	5, 12	3, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	7.4 (2.41)	7.2 (2.61)
Median	7.0	7.0
Q1, Q3	6.0, 9.0	5.0, 9.0
Min, Max	2, 12	1, 12
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	6.8 (2.91)	6.0 (1.75)
Median	7.0	6.0
Q1, Q3	6.0, 8.0	5.0, 6.0
Min, Max	1, 12	3, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	11.1 (1.50)	10.7 (2.12)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	10.0, 12.0
Min, Max	8, 12	4, 12
Gender - Male		
n	19	43
Mean (SD)	10.7 (1.73)	11.1 (1.46)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	7, 12	7, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	10.7 (1.84)	11.0 (1.75)
Median	12.0	12.0
Q1, Q3	9.0, 12.0	10.0, 12.0
Min, Max	7, 12	4, 12
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	11.1 (1.45)	10.9 (1.79)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	7, 12	5, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.

Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	11.2 (1.32)	11.3 (1.47)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	7, 12	5, 12
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	10.6 (1.90)	10.7 (1.95)
Median	12.0	12.0
Q1, Q3	8.5, 12.0	10.0, 12.0
Min, Max	7, 12	4, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	11.1 (1.48)	11.1 (1.56)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	11.0, 12.0
Min, Max	7, 12	5, 12
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	10.6 (1.82)	10.8 (2.06)
Median	12.0	12.0
Q1, Q3	10.0, 12.0	10.0, 12.0
Min, Max	7, 12	4, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	10.5 (1.91)	10.7 (1.90)
Median	12.0	12.0
Q1, Q3	9.0, 12.0	10.0, 12.0
Min, Max	7, 12	4, 12
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	11.5 (0.83)	11.2 (1.54)
Median	12.0	12.0
Q1, Q3	11.0, 12.0	11.0, 12.0
Min, Max	10, 12	5, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSFRS-R domain score by subgroup (observed data) - ITT population

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ALSFRS-R Respiratory Domain Score

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	11.3 (1.51)	11.2 (1.84)
Median	12.0	12.0
Q1, Q3	11.0, 12.0	12.0, 12.0
Min, Max	7, 12	4, 12
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	10.3 (1.65)	10.5 (1.53)
Median	10.0	11.0
Q1, Q3	10.0, 12.0	10.0, 12.0
Min, Max	7, 12	7, 12

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-alsf-dom-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	42.8 (17.47)	37.6 (14.28)
Median	47.0	39.0
Q1, Q3	31.0, 60.0	25.0, 47.0
Min, Max	11, 63	9, 61
Gender - Male		
n	19	43
Mean (SD)	33.1 (14.08)	36.7 (13.60)
Median	30.0	38.0
Q1, Q3	23.0, 46.0	26.0, 45.0
Min, Max	9, 56	13, 63

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	37.5 (13.56)	35.1 (13.20)
Median	43.0	36.5
Q1, Q3	24.0, 48.0	24.0, 43.0
Min, Max	19, 63	13, 61
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	37.8 (18.32)	39.3 (14.27)
Median	39.0	41.5
Q1, Q3	24.0, 53.0	29.0, 49.0
Min, Max	9, 63	9, 63

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	34.1 (17.68)	36.9 (14.80)
Median	31.5	39.0
Q1, Q3	19.0, 49.0	24.0, 47.0
Min, Max	9, 63	9, 63
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	42.1 (13.62)	37.3 (13.00)
Median	46.0	38.0
Q1, Q3	27.5, 50.0	27.0, 47.0
Min, Max	21, 63	13, 61

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	37.1 (15.61)	37.8 (13.65)
Median	39.5	39.0
Q1, Q3	24.0, 50.0	27.0, 47.0
Min, Max	9, 63	9, 61
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	38.6 (17.88)	35.9 (14.18)
Median	39.0	36.0
Q1, Q3	24.0, 53.0	23.0, 47.0
Min, Max	11, 63	14, 63

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	39.0 (14.51)	37.5 (13.04)
Median	43.0	39.0
Q1, Q3	24.0, 49.0	27.0, 47.0
Min, Max	19, 63	13, 61
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	35.8 (18.88)	36.6 (14.80)
Median	39.0	38.0
Q1, Q3	14.0, 53.0	24.0, 47.0
Min, Max	9, 62	9, 63

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline FSS total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	36.7 (17.00)	36.2 (14.65)
Median	43.0	38.0
Q1, Q3	19.0, 50.0	24.0, 45.0
Min, Max	9, 62	13, 63
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	39.4 (15.47)	38.6 (12.24)
Median	35.0	40.0
Q1, Q3	25.0, 50.0	31.0, 47.0
Min, Max	23, 63	9, 59

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	74.1 (13.37)	65.8 (21.65)
Median	75.0	65.0
Q1, Q3	70.0, 80.0	50.0, 85.0
Min, Max	50, 95	27, 100
Gender - Male		
n	19	43
Mean (SD)	73.5 (19.82)	67.5 (18.33)
Median	75.0	70.0
Q1, Q3	60.0, 92.0	60.0, 80.0
Min, Max	30, 100	20, 100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	71.3 (17.85)	70.5 (17.68)
Median	75.0	73.5
Q1, Q3	60.0, 85.0	55.0, 80.0
Min, Max	30, 95	30, 100
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	75.6 (16.30)	62.7 (21.06)
Median	75.0	65.0
Q1, Q3	70.0, 90.0	50.0, 75.0
Min, Max	45, 100	20, 100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	75.7 (19.35)	68.1 (18.56)
Median	76.0	70.0
Q1, Q3	66.5, 92.5	60.0, 80.0
Min, Max	30, 100	30, 100
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	71.4 (13.30)	65.7 (20.67)
Median	72.5	70.0
Q1, Q3	62.5, 77.5	50.0, 80.0
Min, Max	50, 95	20, 100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	75.7 (14.08)	63.0 (18.43)
Median	75.0	68.0
Q1, Q3	70.0, 85.0	50.0, 75.0
Min, Max	45, 100	20, 100
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	70.8 (20.69)	73.2 (20.18)
Median	72.5	80.0
Q1, Q3	60.0, 92.0	60.0, 90.0
Min, Max	30, 99	27, 100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	74.0 (16.84)	64.8 (20.50)
Median	75.0	70.0
Q1, Q3	70.0, 85.0	50.0, 80.0
Min, Max	30, 99	20, 100
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	73.5 (17.45)	69.3 (18.51)
Median	75.0	70.0
Q1, Q3	60.0, 90.0	60.0, 85.0
Min, Max	45, 100	30, 100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline EQ-5D-5L VAS by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	74.1 (16.68)	69.0 (19.52)
Median	75.0	70.0
Q1, Q3	60.0, 90.0	50.0, 80.0
Min, Max	45, 100	27, 100
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	73.2 (17.81)	62.9 (19.51)
Median	75.0	60.0
Q1, Q3	65.0, 85.0	50.0, 75.0
Min, Max	30, 99	20, 91

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5-vas-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	49.85 (10.497)	52.17 (13.850)
Median	50.96	55.12
Q1, Q3	39.94, 60.95	47.11, 61.00
Min, Max	33.8, 63.3	19.7, 72.0
Gender - Male		
n	19	43
Mean (SD)	51.78 (11.347)	50.91 (11.291)
Median	55.34	53.54
Q1, Q3	43.25, 59.16	44.42, 59.68
Min, Max	27.8, 67.5	10.1, 68.8

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	47.92 (10.201)	50.90 (10.989)
Median	50.96	54.34
Q1, Q3	39.94, 56.55	44.81, 59.68
Min, Max	28.6, 60.8	19.7, 67.9
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	52.98 (11.029)	51.99 (13.778)
Median	55.34	54.70
Q1, Q3	44.62, 61.55	45.91, 61.26
Min, Max	27.8, 67.5	10.1, 72.0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	54.97 (8.713)	53.64 (12.897)
Median	56.25	56.38
Q1, Q3	51.66, 61.44	47.11, 61.54
Min, Max	36.8, 67.5	10.1, 72.0
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	45.75 (11.306)	49.43 (11.562)
Median	45.67	53.77
Q1, Q3	37.29, 54.99	40.50, 56.91
Min, Max	27.8, 63.3	19.7, 68.8

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	53.02 (10.113)	51.38 (11.710)
Median	56.25	51.38
Q1, Q3	48.10, 60.80	45.85, 60.28
Min, Max	27.8, 65.6	19.7, 72.0
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	47.50 (11.452)	51.47 (13.474)
Median	46.47	55.12
Q1, Q3	39.28, 55.34	45.91, 60.18
Min, Max	28.6, 67.5	10.1, 68.8

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	49.46 (10.826)	50.15 (11.422)
Median	50.96	54.67
Q1, Q3	41.25, 58.13	43.93, 59.68
Min, Max	28.6, 67.5	19.7, 67.3
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	52.85 (10.920)	52.90 (13.301)
Median	55.34	54.32
Q1, Q3	44.62, 61.55	46.88, 61.55
Min, Max	27.8, 65.6	10.1, 72.0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Mental Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	51.89 (11.295)	50.38 (12.178)
Median	55.34	54.17
Q1, Q3	41.88, 61.32	44.42, 60.16
Min, Max	27.8, 65.6	10.1, 67.9
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	49.07 (10.171)	53.24 (12.562)
Median	50.96	55.46
Q1, Q3	41.25, 55.97	46.88, 61.26
Min, Max	33.8, 67.5	19.7, 72.0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	36.44 (12.405)	32.34 (10.647)
Median	31.48	33.13
Q1, Q3	27.24, 37.71	25.44, 36.86
Min, Max	24.7, 59.0	11.9, 58.9
Gender - Male		
n	19	43
Mean (SD)	35.58 (9.553)	35.70 (8.632)
Median	34.26	36.13
Q1, Q3	29.70, 41.58	29.64, 39.94
Min, Max	20.8, 51.9	17.2, 55.5

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	34.64 (12.199)	37.63 (9.665)
Median	30.24	36.65
Q1, Q3	25.03, 48.68	30.42, 42.67
Min, Max	20.8, 58.4	17.2, 58.9
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	36.95 (9.953)	30.68 (8.124)
Median	34.26	31.50
Q1, Q3	30.08, 39.29	24.98, 36.86
Min, Max	25.8, 59.0	11.9, 43.7

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	39.68 (11.657)	33.97 (9.586)
Median	35.02	34.73
Q1, Q3	30.16, 50.37	28.64, 39.07
Min, Max	25.8, 59.0	15.4, 58.9
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	31.37 (7.811)	34.69 (9.667)
Median	30.13	35.58
Q1, Q3	25.10, 36.23	28.85, 39.94
Min, Max	20.8, 51.3	11.9, 56.2

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	35.22 (10.501)	32.61 (8.015)
Median	31.74	34.05
Q1, Q3	26.67, 41.58	26.70, 36.55
Min, Max	22.0, 58.4	17.2, 58.9
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	37.20 (11.642)	37.25 (11.281)
Median	34.80	38.49
Q1, Q3	30.24, 39.29	30.42, 44.21
Min, Max	20.8, 59.0	11.9, 56.2

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	34.07 (10.439)	34.73 (10.627)
Median	31.43	35.66
Q1, Q3	27.24, 37.71	26.31, 39.84
Min, Max	20.8, 58.4	11.9, 56.2
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	38.67 (11.170)	33.89 (8.285)
Median	35.92	34.05
Q1, Q3	30.08, 49.61	28.83, 39.07
Min, Max	25.8, 59.0	20.5, 58.9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline SF-36 component summary by subgroup (observed data) - ITT population

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Physical Component Summary

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	37.27 (10.911)	37.09 (9.428)
Median	35.79	36.82
Q1, Q3	28.84, 48.68	32.63, 40.76
Min, Max	20.8, 59.0	11.9, 58.9
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	33.72 (10.755)	29.49 (7.851)
Median	31.43	28.94
Q1, Q3	25.77, 35.34	22.26, 35.66
Min, Max	22.0, 58.4	15.4, 44.2

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01SEP2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	23.2 (14.25)	30.0 (15.98)
Median	25.0	30.0
Q1, Q3	15.0, 35.0	20.0, 40.0
Min, Max	0, 45	0, 70
Gender - Male		
n	19	43
Mean (SD)	25.0 (17.32)	26.5 (14.98)
Median	30.0	25.0
Q1, Q3	10.0, 30.0	15.0, 35.0
Min, Max	0, 65	0, 70

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	24.7 (13.56)	24.7 (16.36)
Median	30.0	25.0
Q1, Q3	10.0, 35.0	15.0, 30.0
Min, Max	5, 45	0, 70
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	23.8 (17.46)	31.5 (13.57)
Median	20.0	30.0
Q1, Q3	10.0, 35.0	20.0, 40.0
Min, Max	0, 65	0, 55

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	20.0 (14.05)	25.6 (14.45)
Median	20.0	27.5
Q1, Q3	7.5, 30.0	15.0, 35.0
Min, Max	0, 45	0, 55
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	29.4 (16.62)	30.0 (16.07)
Median	27.5	27.5
Q1, Q3	17.5, 40.0	20.0, 40.0
Min, Max	5, 65	0, 70

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	23.9 (16.40)	27.0 (15.79)
Median	27.5	30.0
Q1, Q3	10.0, 35.0	15.0, 35.0
Min, Max	0, 65	0, 70
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	24.6 (15.25)	29.4 (14.83)
Median	25.0	25.0
Q1, Q3	15.0, 35.0	20.0, 40.0
Min, Max	0, 50	5, 70

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	25.5 (13.87)	29.1 (16.74)
Median	30.0	30.0
Q1, Q3	10.0, 35.0	15.0, 35.0
Min, Max	5, 50	0, 70
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	22.3 (18.41)	26.5 (13.72)
Median	20.0	25.0
Q1, Q3	5.0, 30.0	20.0, 40.0
Min, Max	0, 65	0, 50

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ALSAQ-5 total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	22.6 (15.58)	26.2 (16.30)
Median	25.0	25.0
Q1, Q3	10.0, 30.0	15.0, 35.0
Min, Max	0, 65	0, 70
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	26.9 (16.27)	31.0 (13.34)
Median	30.0	30.0
Q1, Q3	10.0, 40.0	20.0, 40.0
Min, Max	5, 50	10, 55

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: AA negative change indicates better health-Ârelated status.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	87.8 (19.51)	82.4 (17.04)
Median	84.6	79.9
Q1, Q3	70.7, 100.0	68.0, 96.6
Min, Max	55, 120	58, 115
Gender - Male		
n	19	43
Mean (SD)	82.8 (13.42)	81.9 (16.48)
Median	81.3	80.5
Q1, Q3	72.2, 90.3	73.2, 92.1
Min, Max	57, 107	47, 135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	90.1 (16.71)	82.6 (14.52)
Median	89.4	80.2
Q1, Q3	75.8, 102.2	73.5, 95.4
Min, Max	67, 120	47, 115
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	81.6 (15.85)	81.6 (18.84)
Median	81.4	80.1
Q1, Q3	69.3, 90.3	64.1, 96.6
Min, Max	55, 114	55, 135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	87.8 (13.52)	81.5 (16.16)
Median	84.2	83.3
Q1, Q3	79.9, 100.0	68.0, 95.4
Min, Max	67, 114	55, 109
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	81.8 (19.60)	82.6 (17.16)
Median	78.6	79.8
Q1, Q3	68.3, 94.7	72.5, 96.0
Min, Max	55, 120	47, 135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	83.8 (17.67)	81.3 (16.08)
Median	81.6	79.9
Q1, Q3	69.3, 100.0	72.5, 92.1
Min, Max	55, 120	57, 115
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	87.2 (14.94)	83.4 (17.63)
Median	84.3	84.8
Q1, Q3	75.8, 94.9	70.8, 96.0
Min, Max	68, 114	47, 135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	83.7 (17.87)	80.3 (14.22)
Median	81.4	79.8
Q1, Q3	68.5, 94.9	72.5, 91.5
Min, Max	57, 120	47, 115
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	87.1 (14.82)	84.2 (19.02)
Median	84.6	84.8
Q1, Q3	80.2, 100.0	70.8, 98.1
Min, Max	55, 114	55, 135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline percent predicted SVC by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	86.8 (17.11)	83.5 (16.23)
Median	83.9	80.1
Q1, Q3	78.4, 100.0	73.2, 96.3
Min, Max	55, 120	55, 135
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	82.2 (15.69)	79.5 (17.22)
Median	80.2	80.4
Q1, Q3	68.5, 89.4	64.1, 91.7
Min, Max	67, 114	47, 115

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A higher score or a positive change indicates an improvement. The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
Abbreviations: SVC = slow vital capacity.
Source: biib067/valueaccess/amnog/t-cf-svc-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	0.0 (0.67)	-0.4 (0.40)
Median	-0.2	-0.5
Q1, Q3	-0.5, 0.2	-0.7, -0.2
Min, Max	-1, 2	-1, 0
Gender - Male		
n	19	43
Mean (SD)	0.1 (0.52)	0.2 (0.90)
Median	0.2	0.0
Q1, Q3	-0.1, 0.5	-0.4, 0.7
Min, Max	-1, 1	-1, 3

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	0.0 (0.59)	0.2 (0.74)
Median	-0.1	0.0
Q1, Q3	-0.5, 0.6	-0.2, 0.5
Min, Max	-1, 1	-1, 2
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	0.1 (0.61)	-0.3 (0.81)
Median	-0.1	-0.5
Q1, Q3	-0.2, 0.4	-0.7, 0.0
Min, Max	-1, 2	-1, 3

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	0.3 (0.54)	0.0 (0.98)
Median	0.2	-0.3
Q1, Q3	-0.1, 0.5	-0.6, 0.2
Min, Max	0, 2	-1, 3
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	-0.2 (0.56)	0.0 (0.60)
Median	-0.3	-0.1
Q1, Q3	-0.6, 0.1	-0.5, 0.2
Min, Max	-1, 1	-1, 2

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	0.0 (0.68)	-0.2 (0.69)
Median	-0.1	-0.3
Q1, Q3	-0.5, 0.2	-0.6, 0.1
Min, Max	-1, 2	-1, 2
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	0.2 (0.42)	0.2 (0.92)
Median	0.2	0.0
Q1, Q3	-0.2, 0.5	-0.5, 0.5
Min, Max	-1, 1	-1, 3

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	0.0 (0.60)	0.0 (0.67)
Median	-0.1	-0.1
Q1, Q3	-0.5, 0.5	-0.5, 0.4
Min, Max	-1, 1	-1, 2
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	0.1 (0.60)	-0.1 (0.94)
Median	-0.1	-0.3
Q1, Q3	-0.2, 0.4	-0.6, 0.0
Min, Max	-1, 2	-1, 3

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline HHD overall megascore by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	0.1 (0.64)	0.1 (0.86)
Median	-0.1	-0.1
Q1, Q3	-0.3, 0.4	-0.5, 0.4
Min, Max	-1, 2	-1, 3
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	0.0 (0.53)	-0.3 (0.62)
Median	-0.1	-0.5
Q1, Q3	-0.2, 0.5	-0.6, 0.0
Min, Max	-1, 1	-1, 2

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
Abbreviations: HHD = handheld dynamometry.
Source: biib067/valueaccess/amnog/t-cf-mega-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	12	22
Mean (SD)	17.6 (8.80)	19.2 (13.61)
Median	18.0	13.5
Q1, Q3	11.0, 23.0	11.0, 26.0
Min, Max	4, 34	2, 61
Gender - Male		
n	13	31
Mean (SD)	19.5 (12.59)	17.9 (11.72)
Median	16.8	13.0
Q1, Q3	12.0, 25.0	8.0, 26.0
Min, Max	3, 53	2, 50

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	12	27
Mean (SD)	16.3 (8.63)	15.6 (9.22)
Median	16.4	13.0
Q1, Q3	10.5, 21.5	9.0, 20.0
Min, Max	4, 34	2, 39
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	13	26
Mean (SD)	20.7 (12.38)	21.4 (14.66)
Median	19.0	16.5
Q1, Q3	12.0, 25.0	11.0, 30.0
Min, Max	3, 53	2, 61

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	13	25
Mean (SD)	16.2 (8.75)	17.6 (9.91)
Median	15.0	14.0
Q1, Q3	11.0, 22.0	11.0, 25.0
Min, Max	3, 31	2, 40
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	12	28
Mean (SD)	21.2 (12.42)	19.2 (14.45)
Median	18.0	13.0
Q1, Q3	14.0, 25.0	9.5, 26.5
Min, Max	6, 53	2, 61

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	15	34
Mean (SD)	19.5 (12.44)	19.9 (13.54)
Median	19.0	15.0
Q1, Q3	11.0, 25.0	11.0, 26.0
Min, Max	3, 53	2, 61
Riluzole or edaravone use - Neither		
n	10	19
Mean (SD)	17.3 (8.04)	15.8 (9.93)
Median	16.4	12.0
Q1, Q3	11.0, 22.0	8.0, 26.0
Min, Max	6, 31	2, 35

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	17	30
Mean (SD)	16.9 (8.31)	18.6 (12.73)
Median	16.8	14.5
Q1, Q3	11.0, 20.0	10.0, 26.0
Min, Max	4, 34	6, 61
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	8	23
Mean (SD)	22.1 (14.76)	18.3 (12.30)
Median	20.5	13.0
Q1, Q3	13.5, 26.5	9.0, 27.0
Min, Max	3, 53	2, 50

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline ZBI total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	13	31
Mean (SD)	20.2 (12.40)	15.5 (9.77)
Median	17.0	12.0
Q1, Q3	15.0, 19.0	8.0, 20.0
Min, Max	3, 53	2, 40
Age at first dose - >= 55 years		
n	12	22
Mean (SD)	16.8 (8.84)	22.7 (14.63)
Median	16.0	19.0
Q1, Q3	10.5, 24.5	13.0, 30.0
Min, Max	4, 31	5, 61

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: All data are used regardless of change in caregiver. Subjects who do not have a caregiver at baseline are not included. A positive change indicates greater caregiver distress.
Abbreviations: ZBI = Zarit Burden Interview.
Source: biib067/valueaccess/amnog/t-cf-zbi-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	29.6 (1.00)	29.6 (0.73)
Median	30.0	30.0
Q1, Q3	30.0, 30.0	29.0, 30.0
Min, Max	26, 30	28, 30
Gender - Male		
n	19	43
Mean (SD)	29.2 (1.54)	29.4 (1.28)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	25, 30	24, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	29.3 (1.29)	29.4 (1.16)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	26, 30	24, 30
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	29.4 (1.36)	29.5 (1.02)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	25, 30	25, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	29.5 (1.19)	29.3 (1.39)
Median	30.0	30.0
Q1, Q3	29.5, 30.0	29.0, 30.0
Min, Max	25, 30	24, 30
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	29.2 (1.47)	29.6 (0.72)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	26, 30	28, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	29.3 (1.46)	29.5 (1.06)
Median	30.0	30.0
Q1, Q3	30.0, 30.0	29.0, 30.0
Min, Max	25, 30	24, 30
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	29.4 (1.09)	29.4 (1.15)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	26, 30	25, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	29.3 (1.35)	29.4 (1.16)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	26, 30	24, 30
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	29.5 (1.30)	29.5 (1.00)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	25, 30	25, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline MMSE total score by subgroup (observed data) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	29.2 (1.51)	29.5 (1.24)
Median	30.0	30.0
Q1, Q3	29.0, 30.0	29.0, 30.0
Min, Max	25, 30	24, 30
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	29.6 (0.87)	29.5 (0.76)
Median	30.0	30.0
Q1, Q3	30.0, 30.0	29.0, 30.0
Min, Max	27, 30	28, 30

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
Abbreviations: MMSE = Mini-Mental State Examination.
Source: biib067/valueaccess/amnog/t-mmse-tot-base-sgrp.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31AUG2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	4.7 (2.73)	6.3 (2.61)
Median	6.0	7.0
Q1, Q3	3.0, 6.0	5.0, 8.0
Min, Max	0, 8	0, 10
Gender - Male		
n	19	43
Mean (SD)	4.8 (2.63)	4.9 (2.44)
Median	5.0	5.0
Q1, Q3	3.0, 7.0	3.0, 7.0
Min, Max	0, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	5.4 (2.64)	5.0 (2.64)
Median	6.0	5.0
Q1, Q3	3.0, 8.0	3.0, 7.0
Min, Max	0, 10	0, 10
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	4.3 (2.61)	5.9 (2.47)
Median	5.0	6.5
Q1, Q3	3.0, 6.0	4.0, 8.0
Min, Max	0, 8	1, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	3.8 (2.84)	5.3 (2.79)
Median	3.0	5.0
Q1, Q3	1.5, 6.5	3.0, 8.0
Min, Max	0, 8	0, 10
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	6.0 (1.79)	5.6 (2.41)
Median	6.0	5.0
Q1, Q3	5.0, 7.0	3.9, 8.0
Min, Max	3, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	4.8 (2.61)	5.6 (2.54)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.9, 8.0
Min, Max	0, 10	0, 10
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	4.7 (2.79)	5.1 (2.68)
Median	4.5	5.0
Q1, Q3	3.0, 8.0	2.0, 8.0
Min, Max	0, 8	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	5.3 (2.37)	5.6 (2.56)
Median	6.0	5.0
Q1, Q3	4.0, 6.0	3.0, 8.0
Min, Max	0, 10	1, 10
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	4.0 (2.88)	5.2 (2.63)
Median	4.0	5.0
Q1, Q3	1.0, 7.0	3.0, 8.0
Min, Max	0, 8	0, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	4.6 (2.35)	5.0 (2.65)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.0, 8.0
Min, Max	0, 8	0, 10
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	5.1 (3.17)	6.2 (2.31)
Median	5.0	6.6
Q1, Q3	3.0, 8.0	5.0, 8.0
Min, Max	0, 10	2, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Gender - Female		
n	17	29
Mean (SD)	4.7 (2.73)	6.2 (2.63)
Median	6.0	7.0
Q1, Q3	3.0, 6.0	5.0, 8.0
Min, Max	0, 8	0, 10
Gender - Male		
n	19	43
Mean (SD)	4.8 (2.63)	4.9 (2.44)
Median	5.0	5.0
Q1, Q3	3.0, 7.0	3.0, 7.0
Min, Max	0, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	5.4 (2.64)	5.0 (2.65)
Median	6.0	5.0
Q1, Q3	3.0, 8.0	3.0, 7.0
Min, Max	0, 10	0, 10
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	4.3 (2.61)	5.9 (2.47)
Median	5.0	6.5
Q1, Q3	3.0, 6.0	4.0, 8.0
Min, Max	0, 8	1, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	3.8 (2.84)	5.3 (2.79)
Median	3.0	5.0
Q1, Q3	1.5, 6.5	3.0, 8.0
Min, Max	0, 8	0, 10
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	6.0 (1.79)	5.6 (2.42)
Median	6.0	5.0
Q1, Q3	5.0, 7.0	3.7, 8.0
Min, Max	3, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	4.8 (2.61)	5.6 (2.54)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.7, 8.0
Min, Max	0, 10	0, 10
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	4.7 (2.79)	5.1 (2.68)
Median	4.5	5.0
Q1, Q3	3.0, 8.0	2.0, 8.0
Min, Max	0, 8	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	5.3 (2.37)	5.6 (2.57)
Median	6.0	5.0
Q1, Q3	4.0, 6.0	3.0, 8.0
Min, Max	0, 10	1, 10
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	4.0 (2.88)	5.2 (2.63)
Median	4.0	5.0
Q1, Q3	1.0, 7.0	3.0, 8.0
Min, Max	0, 8	0, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of baseline WPAI-Q6 by subgroup using MI (adjusting for baseline plasma NfL) - ITT population

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Subgroup	placebo (N=36)	tofersen 100 mg (N=72)
Age at first dose - < 55 years		
n	23	46
Mean (SD)	4.6 (2.35)	5.0 (2.65)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.0, 8.0
Min, Max	0, 8	0, 10
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	5.1 (3.17)	6.2 (2.33)
Median	5.0	6.6
Q1, Q3	3.0, 8.0	5.0, 8.0
Min, Max	0, 10	2, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-bnfl-sgrp-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Gender - Female		
n	17	29
Mean (SD)	4.7 (2.73)	6.2 (2.63)
Median	6.0	7.0
Q1, Q3	3.0, 6.0	5.0, 8.0
Min, Max	0, 8	0, 10
Gender - Male		
n	19	43
Mean (SD)	4.8 (2.63)	4.9 (2.44)
Median	5.0	5.0
Q1, Q3	3.0, 7.0	3.0, 7.0
Min, Max	0, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Baseline disease duration since symptom onset by median - < Median (11.79 months)		
n	15	38
Mean (SD)	5.4 (2.64)	5.0 (2.65)
Median	6.0	5.0
Q1, Q3	3.0, 8.0	3.0, 7.0
Min, Max	0, 10	0, 10
Baseline disease duration since symptom onset by median - >= Median (11.79 months)		
n	21	34
Mean (SD)	4.3 (2.61)	5.9 (2.47)
Median	5.0	6.5
Q1, Q3	3.0, 6.0	4.0, 8.0
Min, Max	0, 8	1, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Baseline plasma NfL by median - < Median (75.60 pg/mL)		
n	20	34
Mean (SD)	3.8 (2.84)	5.3 (2.79)
Median	3.0	5.0
Q1, Q3	1.5, 6.5	3.0, 8.0
Min, Max	0, 8	0, 10
Baseline plasma NfL by median - >= Median (75.60 pg/mL)		
n	16	38
Mean (SD)	6.0 (1.79)	5.6 (2.42)
Median	6.0	5.0
Q1, Q3	5.0, 7.0	3.7, 8.0
Min, Max	3, 10	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Riluzole or edaravone use - Edaravone or Riluzole Use		
n	22	45
Mean (SD)	4.8 (2.61)	5.6 (2.54)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.7, 8.0
Min, Max	0, 10	0, 10
Riluzole or edaravone use - Neither		
n	14	27
Mean (SD)	4.7 (2.79)	5.1 (2.68)
Median	4.5	5.0
Q1, Q3	3.0, 8.0	2.0, 8.0
Min, Max	0, 8	1, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Prognostic enrichment criteria for rapid disease progression - mITT population		
n	21	39
Mean (SD)	5.3 (2.37)	5.6 (2.57)
Median	6.0	5.0
Q1, Q3	4.0, 6.0	3.0, 8.0
Min, Max	0, 10	1, 10
Prognostic enrichment criteria for rapid disease progression - non mITT population		
n	15	33
Mean (SD)	4.0 (2.88)	5.2 (2.63)
Median	4.0	5.0
Q1, Q3	1.0, 7.0	3.0, 8.0
Min, Max	0, 8	0, 9

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 and 233AS102 ISE: Summary of baseline WPAI-Q6 by subgroup using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
Subgroup	**(N=36)**	**(N=72)**
Age at first dose - < 55 years		
n	23	46
Mean (SD)	4.6 (2.35)	5.0 (2.65)
Median	5.0	5.0
Q1, Q3	3.0, 6.0	3.0, 8.0
Min, Max	0, 8	0, 10
Age at first dose - >= 55 years		
n	13	26
Mean (SD)	5.1 (3.17)	6.2 (2.33)
Median	5.0	6.6
Q1, Q3	3.0, 8.0	5.0, 8.0
Min, Max	0, 10	2, 10

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-wpa-base-mi-sgrp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07SEP2023

233AS101 Part C: Summary of time to death or permanent ventilation: treatment by subgroup interaction - ITT population

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Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.6226
Baseline disease duration since symptom onset by median	0.6436
Baseline NfL plasma level (< 75.60 pg/mL, >= 75.60 pg/mL)	1.0000
Riluzole or edaravone use	0.6922
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.9998
Age at first dose (<55, >=55)	0.9958

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
NOTE 2: P-value is based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The model dose not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-tte-subgrp-inter.sas:t-tte-subgrp-inter-tdvafs.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 08FEB2023

233AS101 Part C: Summary of time to permanent ventilation: treatment by subgroup interaction - ITT population

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Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.9958
Baseline disease duration since symptom onset by median	0.7300
Baseline NfL plasma level (< 75.60 pg/mL, >= 75.60 pg/mL)	1.0000
Riluzole or edaravone use	0.8401
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.9998
Age at first dose (<55, >=55)	0.9957

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
NOTE 2: Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, riluzole or edaravone use and treatment by subgroup interaction. The model dose not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-tte-subgrp-inter.sas:t-tte-subgrp-inter-tvafs.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 08FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by gender - ITT population

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Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with an event of death or permanent ventilation	1 (5.9)	3 (10.3)
Death	0	0
Permanent ventilation	1 (5.9)	3 (10.3)
Number of subjects who were censored	16 (94.1)	26 (89.7)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	194.0 (NE, NE)
10th percentile	NE (192.0, NE)	196.0 (114.0, NE)
25th percentile	NE (192.0, NE)	NE (194.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by gender - ITT population

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Female

	placebo (N=17)	tofersen 100 mg (N=29)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.063	0.132
p-value (tofersen - placebo) (b)		0.5244
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.35 (0.098, 18.590)
p-value (tofersen - placebo) (c)		0.8218

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by gender - ITT population

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Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with an event of death or permanent ventilation	[redacted]	[redacted]
Death	0	1 (2.3)
Permanent ventilation	[redacted]	[redacted]
Number of subjects who were censored	18 (94.7)	42 (97.7)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (114.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by gender - ITT population

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Male

	placebo (N=19)	tofersen 100 mg (N=43)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.059	0.024
p-value (tofersen - placebo) (b)		0.5352
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.51 (0.030, 8.459)
p-value (tofersen - placebo) (c)		0.6349

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with an event of death or permanent ventilation	1 (6.7)	3 (7.9)
Death	0	1 (2.6)
Permanent ventilation	1 (6.7)	2 (5.3)
Number of subjects who were censored	14 (93.3)	35 (92.1)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	114.0 (NE, NE)
10th percentile	NE (192.0, NE)	NE (114.0, NE)
25th percentile	NE (192.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.077	0.082
p-value (tofersen - placebo) (b)		0.7451
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.29 (0.100, 16.540)
p-value (tofersen - placebo) (c)		0.8473

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with an event of death or permanent ventilation	1 (4.8)	1 (2.9)
Death	0	0
Permanent ventilation	1 (4.8)	1 (2.9)
Number of subjects who were censored	20 (95.2)	33 (97.1)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (194.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.050	0.034
p-value (tofersen - placebo) (b)		0.8236
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.92 (0.055, 15.216)
p-value (tofersen - placebo) (c)		0.9519

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with an event of death or permanent ventilation	0	0
Death	0	0
Permanent ventilation	0	0
Number of subjects who were censored	20 (100.0)	34 (100.0)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	NE (NE, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.000	0.000
p-value (tofersen - placebo) (b)		NE
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with an event of death or permanent ventilation	2 (12.5)	4 (10.5)
Death	0	1 (2.6)
Permanent ventilation	2 (12.5)	3 (7.9)
Number of subjects who were censored	14 (87.5)	34 (89.5)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	114.0 (NE, NE)
10th percentile	192.0 (171.0, NE)	196.0 (114.0, NE)
25th percentile	NE (171.0, NE)	NE (196.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by baseline plasma NfL level (median) - ITT population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.143	0.114
p-value (tofersen - placebo) (b)		0.7863
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.80 (0.130, 4.934)
p-value (tofersen - placebo) (c)		0.8118

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with an event of death or permanent ventilation	1 (4.5)	1 (2.2)
Death	0	0
Permanent ventilation	1 (4.5)	1 (2.2)
Number of subjects who were censored	21 (95.5)	44 (97.8)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (196.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.048	0.028
p-value (tofersen - placebo) (b)		0.5959
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.47 (0.029, 7.624)
p-value (tofersen - placebo) (c)		0.5958

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by riluzole or edaravone use - ITT population

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Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with an event of death or permanent ventilation	1 (7.1)	3 (11.1)
Death	0	1 (3.7)
Permanent ventilation	1 (7.1)	2 (7.4)
Number of subjects who were censored	13 (92.9)	24 (88.9)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	114.0 (NE, NE)
10th percentile	NE (192.0, NE)	194.0 (114.0, NE)
25th percentile	NE (192.0, NE)	NE (114.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by riluzole or edaravone use - ITT population

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Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.083	0.121
p-value (tofersen - placebo) (b)		0.6677
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.85 (0.069, 10.533)
p-value (tofersen - placebo) (c)		0.9015

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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MITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with an event of death or permanent ventilation	2 (9.5)	4 (10.3)
Death	0	1 (2.6)
Permanent ventilation	2 (9.5)	3 (7.7)
Number of subjects who were censored	19 (90.5)	35 (89.7)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	114.0 (NE, NE)
10th percentile	192.0 (171.0, NE)	196.0 (114.0, NE)
25th percentile	NE (171.0, NE)	NE (196.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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MITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.105	0.111
p-value (tofersen - placebo) (b)		0.7682
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.67 (0.245, 11.379)
p-value (tofersen - placebo) (c)		0.5997

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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Non-MITT Population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with an event of death or permanent ventilation	0	0
Death	0	0
Permanent ventilation	0	0
Number of subjects who were censored	15 (100.0)	33 (100.0)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	NE (NE, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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Non-MITT Population

	placebo (N=15)	tofersen 100 mg (N=33)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.000	0.000
p-value (tofersen - placebo) (b)		NE
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by age at first dose - ITT population

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<55 Years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with an event of death or permanent ventilation	2 (8.7)	2 (4.3)
Death	0	0
Permanent ventilation	2 (8.7)	2 (4.3)
Number of subjects who were censored	21 (91.3)	44 (95.7)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (114.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by age at first dose - ITT population

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<55 Years

	placebo (N=23)	tofersen 100 mg (N=46)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	0.095	0.045
p-value (tofersen - placebo) (b)		0.3648
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.08 (0.005, 1.380)

p-value (tofersen - placebo) (c)	0.0821

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by age at first dose - ITT population

>=55 Years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with an event of death or permanent ventilation	[redacted]	[redacted]
Death	0	1 (3.8)
Permanent ventilation	[redacted]	[redacted]
Number of subjects who were censored	13 (100.0)	24 (92.3)
Time to death or permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	196.0 (114.0, NE)
25th percentile	NE (NE, NE)	NE (114.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to death or permanent ventilation by age at first dose - ITT population

>=55 Years

	placebo (N=13)	tofersen 100 mg (N=26)
Estimated proportion (a) of subjects with an event of death or permanent ventilation by 197 days	[redacted]	
p-value (tofersen - placebo) (b)		0.2467
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafs-sum.sas:t-cf-vafs-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 07FEB2023

233AS101 Part C: Summary of time to permanent ventilation by gender - ITT population

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Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with permanent ventilation	1 (5.9)	3 (10.3)
Number of subjects who were censored	16 (94.1)	26 (89.7)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	194.0 (NE, NE)
10th percentile	NE (192.0, NE)	196.0 (114.0, NE)
25th percentile	NE (192.0, NE)	NE (194.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by gender - ITT population

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Female

	placebo (N=17)	tofersen 100 mg (N=29)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.063	0.132
p-value (tofersen - placebo) (b)		0.5244
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.35 (0.098, 18.590)
p-value (tofersen - placebo) (c)		0.8218

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by gender - ITT population

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Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with permanent ventilation	[redacted]	
Number of subjects who were censored	18 (94.7)	43 (100.0)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (NE, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by gender - ITT population

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Male

	placebo (N=19)	tofersen 100 mg (N=43)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	[redacted]	
p-value (tofersen - placebo) (b)		0.1213
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.00 (0.000, NE)
p-value (tofersen - placebo) (c)		0.9986

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-gender.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with permanent ventilation	1 (6.7)	2 (5.3)
Number of subjects who were censored	14 (93.3)	36 (94.7)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	196.0 (NE, NE)
10th percentile	NE (192.0, NE)	NE (114.0, NE)
25th percentile	NE (192.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.077	0.057
p-value (tofersen - placebo) (b)		0.9702
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.19 (0.081, 17.457)
p-value (tofersen - placebo) (c)		0.8983

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with permanent ventilation	1 (4.8)	1 (2.9)
Number of subjects who were censored	20 (95.2)	33 (97.1)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (194.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.050	0.034
p-value (tofersen - placebo) (b)		0.8236
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.92 (0.055, 15.216)
p-value (tofersen - placebo) (c)		0.9519

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bddurmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with permanent ventilation	0	0
Number of subjects who were censored	20 (100.0)	34 (100.0)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	NE (NE, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.000	0.000
p-value (tofersen - placebo) (b)		NE
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with permanent ventilation	2 (12.5)	3 (7.9)
Number of subjects who were censored	14 (87.5)	35 (92.1)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	194.0 (NE, NE)
10th percentile	192.0 (171.0, NE)	NE (114.0, NE)
25th percentile	NE (171.0, NE)	NE (196.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.143	0.089
p-value (tofersen - placebo) (b)		0.6018
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.68 (0.098, 4.772)
p-value (tofersen - placebo) (c)		0.7012

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-bpnflmed.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by riluzole or edaravone use - ITT population

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Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with permanent ventilation	1 (4.5)	1 (2.2)
Number of subjects who were censored	21 (95.5)	44 (97.8)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (196.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by riluzole or edaravone use - ITT population

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Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.048	0.028
p-value (tofersen - placebo) (b)		0.5959
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.47 (0.029, 7.624)
p-value (tofersen - placebo) (c)		0.5958

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by riluzole or edaravone use - ITT population

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Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with permanent ventilation	1 (7.1)	2 (7.4)
Number of subjects who were censored	13 (92.9)	25 (92.6)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	194.0 (NE, NE)
10th percentile	NE (192.0, NE)	NE (114.0, NE)
25th percentile	NE (192.0, NE)	NE (194.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by riluzole or edaravone use - ITT population

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Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.083	0.084
p-value (tofersen - placebo) (b)		0.9447
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.20 (0.003, 15.678)
p-value (tofersen - placebo) (c)		0.4734

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-edruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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MITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with permanent ventilation	2 (9.5)	3 (7.7)
Number of subjects who were censored	19 (90.5)	36 (92.3)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	171.0 (NE, NE)	194.0 (NE, NE)
10th percentile	192.0 (171.0, NE)	NE (114.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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MITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.105	0.086
p-value (tofersen - placebo) (b)		0.9881
Hazard ratio (tofersen - placebo) and 95% CI (c)		1.41 (0.182, 10.844)
p-value (tofersen - placebo) (c)		0.7434

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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Non-MITT Population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with permanent ventilation	0	0
Number of subjects who were censored	15 (100.0)	33 (100.0)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	NE (NE, NE)
10th percentile	NE (NE, NE)	NE (NE, NE)
25th percentile	NE (NE, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by prognostic enrichment criteria for rapid disease progression - ITT population

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Non-MITT Population

	placebo (N=15)	tofersen 100 mg (N=33)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.000	0.000
p-value (tofersen - placebo) (b)		NE
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-progcrit.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by age at first dose - ITT population

<55 Years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with permanent ventilation	2 (8.7)	2 (4.3)
Number of subjects who were censored	21 (91.3)	44 (95.7)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	192.0 (NE, NE)	NE (NE, NE)
10th percentile	NE (171.0, NE)	NE (114.0, NE)
25th percentile	NE (171.0, NE)	NE (NE, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by riluzole or edaravone use.
(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.
Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by age at first dose - ITT population

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<55 Years

	placebo (N=23)	tofersen 100 mg (N=46)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	0.095	0.045
p-value (tofersen - placebo) (b)		0.3648
Hazard ratio (tofersen - placebo) and 95% CI (c)		0.08 (0.005, 1.380)
p-value (tofersen - placebo) (c)		0.0821

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by age at first dose - ITT population

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>=55 Years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with permanent ventilation	[redacted]	
Number of subjects who were censored	13 (100.0)	25 (96.2)
Time to permanent ventilation (95% CI) (Days) (a)		
5th percentile	NE (NE, NE)	196.0 (NE, NE)
10th percentile	NE (NE, NE)	NE (196.0, NE)
25th percentile	NE (NE, NE)	NE (196.0, NE)
50th percentile	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: Summary of time to permanent ventilation by age at first dose - ITT population

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>=55 Years

	placebo (N=13)	tofersen 100 mg (N=26)
Estimated proportion (a) of subjects with permanent ventilation by 197 days	[redacted]	
p-value (tofersen - placebo) (b)		0.4795
Hazard ratio (tofersen - placebo) and 95% CI (c)		NE
p-value (tofersen - placebo) (c)		NE

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored on the date of subject's last contact in Study 233AS101. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Subjects may have events started in 233AS101 and continued into 233AS102.

(a) Based on Kaplan-Meier product limit method.

(b) Based on a log rank test stratified by riluzole or edaravone use.

(c) Based on a Cox proportional hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, and riluzole or edaravone use.

Abbreviations: EAC = Endpoint Adjudication Committee; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-vafsp-sum.sas:t-cf-vafsp-sum-agegrp.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 06FEB2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.1925
Baseline disease duration since symptom onset by median	0.4809
Baseline NfL plasma level by median	0.1843
Riluzole or edaravone use	0.6460
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.9048
Age at first dose (<55, >=55)	0.0798

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	16 (94.1)	23 (79.3)
Number of imputed values per imputation	1 (5.9)	6 (20.7)
LS mean change from baseline	-4.4	-5.1
SE	1.79	1.46
95% CI	(-7.88, -0.86)	(-7.96, -2.25)
LS mean difference (tofersen - placebo)		-0.7
SE		2.15
95% CI		(-4.94, 3.48)
p-value		0.7326
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.68, 0.60)
p-value		0.9087

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	17 (89.5)	40 (93.0)
Number of imputed values per imputation	2 (10.5)	3 (7.0)
LS mean change from baseline	-6.4	-3.4
SE	1.94	1.58
95% CI	(-10.23, -2.63)	(-6.54, -0.34)
LS mean difference (tofersen - placebo)		3.0
SE		1.88
95% CI		(-0.69, 6.68)
p-value		0.1111
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.14, 1.01)
p-value		0.1380

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-8.1	-7.3
SE	2.34	1.80
95% CI	(-12.68, -3.51)	(-10.79, -3.74)
LS mean difference (tofersen - placebo)		0.8
SE		2.40
95% CI		(-3.86, 5.53)
p-value		0.7279
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.57, 0.71)
p-value		0.8208

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	20 (95.2)	29 (85.3)
Number of imputed values per imputation	1 (4.8)	5 (14.7)
LS mean change from baseline	-4.6	-1.5
SE	1.48	1.22
95% CI	(-7.48, -1.69)	(-3.90, 0.87)
LS mean difference (tofersen - placebo)		3.1
SE		1.73
95% CI		(-0.33, 6.47)
p-value		0.0769
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.11, 1.05)
p-value		0.1115

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	19 (95.0)	30 (88.2)
Number of imputed values per imputation	1 (5.0)	4 (11.8)
LS mean change from baseline	-1.8	-1.2
SE	0.81	0.70
95% CI	(-3.40, -0.22)	(-2.56, 0.19)
LS mean difference (tofersen - placebo)		0.6
SE		1.00
95% CI		(-1.33, 2.58)
p-value		0.5281
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.27, 0.89)
p-value		0.2918

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	14 (87.5)	33 (86.8)
Number of imputed values per imputation	2 (12.5)	5 (13.2)
LS mean change from baseline	-11.3	-7.3
SE	2.45	1.92
95% CI	(-16.06, -6.46)	(-11.10, -3.57)
LS mean difference (tofersen - placebo)		3.9
SE		2.52
95% CI		(-1.00, 8.86)
p-value		0.1184
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.24, 1.02)
p-value		0.2233

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	21 (95.5)	42 (93.3)
Number of imputed values per imputation	1 (4.5)	3 (6.7)
LS mean change from baseline	-4.4	-3.6
SE	1.27	0.90
95% CI	(-6.94, -1.94)	(-5.32, -1.78)
LS mean difference (tofersen - placebo)		0.9
SE		1.57
95% CI		(-2.18, 3.96)
p-value		0.5701
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.33, 0.72)
p-value		0.4685

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R total score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	21 (77.8)
Number of imputed values per imputation	2 (14.3)	6 (22.2)
LS mean change from baseline	-7.6	-5.3
SE	2.14	1.61
95% CI	(-11.75, -3.38)	(-8.49, -2.20)
LS mean difference (tofersen - placebo)		2.2
SE		2.66
95% CI		(-2.99, 7.44)
p-value		0.4038
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.49, 0.94)
p-value		0.5336

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R total score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-8.6	-7.5
SE	2.23	1.90
95% CI	(-13.01, -4.25)	(-11.18, -3.73)
LS mean difference (tofersen - placebo)		1.2
SE		2.23
95% CI		(-3.19, 5.55)
p-value		0.5979
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.40, 0.73)
p-value		0.5662

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	14 (93.3)	30 (90.9)
Number of imputed values per imputation	1 (6.7)	3 (9.1)
LS mean change from baseline	-2.7	-1.3
SE	1.10	0.80
95% CI	(-4.88, -0.58)	(-2.91, 0.24)
LS mean difference (tofersen - placebo)		1.4
SE		1.28
95% CI		(-1.10, 3.90)
p-value		0.2726
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.35, 0.92)
p-value		0.3808

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	21 (91.3)	42 (91.3)
Number of imputed values per imputation	2 (8.7)	4 (8.7)
LS mean change from baseline	-6.7	-3.6
SE	1.68	1.27
95% CI	(-9.97, -3.39)	(-6.08, -1.10)
LS mean difference (tofersen - placebo)		3.1
SE		1.79
95% CI		(-0.41, 6.60)
p-value		0.0837
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.18, 0.88)
p-value		0.1933

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	21 (80.8)
Number of imputed values per imputation	1 (7.7)	5 (19.2)
LS mean change from baseline	-4.0	-6.1
SE	2.10	1.67
95% CI	(-8.09, 0.12)	(-9.39, -2.84)
LS mean difference (tofersen - placebo)		-2.1
SE		2.33
95% CI		(-6.70, 2.44)
p-value		0.3606
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.75, 0.67)
p-value		0.9135

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-anc-mi-sgrp.sas:t-cf-alsf-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Bulbar Function Domain Score

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.0733
Baseline disease duration since symptom onset by median	0.1752
Baseline NfL plasma level by median	0.3490
Riluzole or edaravone use	0.9155
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1776
Age at first dose (<55, >=55)	0.2121

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R domain score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Fine Motor Skill Domain Score

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.5410
Baseline disease duration since symptom onset by median	0.9999
Baseline NfL plasma level by median	0.0138
Riluzole or edaravone use	0.9042
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.2775
Age at first dose (<55, >=55)	0.0863

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R domain score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Gross Motor Skill Domain Score

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.1192
Baseline disease duration since symptom onset by median	0.9159
Baseline NfL plasma level by median	0.3379
Riluzole or edaravone use	0.0985
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3933
Age at first dose (<55, >=55)	0.3084

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R domain score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Respiratory Domain Score

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.4097
Baseline disease duration since symptom onset by median	0.4766
Baseline NfL plasma level by median	0.3121
Riluzole or edaravone use	0.8869
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.7021
Age at first dose (<55, >=55)	0.1362

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R domain score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Bulbar Function Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	16 (94.1)	23 (79.3)
Number of imputed values per imputation	1 (5.9)	6 (20.7)
LS mean change from baseline	-0.1	-1.0
SE	0.39	0.32
95% CI	(-0.89, 0.63)	(-1.61, -0.35)
LS mean difference (tofersen - placebo)		-0.8
SE		0.47
95% CI		(-1.77, 0.07)
p-value		0.0715
Hedge's g standardized mean difference (tofersen - placebo)		-0.5
95% CI		(-1.18, 0.12)
p-value		0.1106

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Bulbar Function Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	17 (89.5)	40 (93.0)
Number of imputed values per imputation	2 (10.5)	3 (7.0)
LS mean change from baseline	-0.6	-0.5
SE	0.39	0.32
95% CI	(-1.41, 0.13)	(-1.11, 0.16)
LS mean difference (tofersen - placebo)		0.2
SE		0.38
95% CI		(-0.59, 0.92)
p-value		0.6694
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.75)
p-value		0.5220

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	16 (94.1)	23 (79.3)
Number of imputed values per imputation	1 (5.9)	6 (20.7)
LS mean change from baseline	-1.7	-1.2
SE	0.56	0.45
95% CI	(-2.75, -0.56)	(-2.09, -0.31)
LS mean difference (tofersen - placebo)		0.5
SE		0.67
95% CI		(-0.86, 1.77)
p-value		0.4994
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.37, 0.91)
p-value		0.4025

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	17 (89.5)	40 (93.0)
Number of imputed values per imputation	2 (10.5)	3 (7.0)
LS mean change from baseline	-2.2	-1.2
SE	0.66	0.54
95% CI	(-3.47, -0.86)	(-2.28, -0.17)
LS mean difference (tofersen - placebo)		0.9
SE		0.64
95% CI		(-0.31, 2.20)
p-value		0.1410
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.22, 0.92)
p-value		0.2307

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	16 (94.1)	23 (79.3)
Number of imputed values per imputation	1 (5.9)	6 (20.7)
LS mean change from baseline	-1.4	-1.1
SE	0.46	0.37
95% CI	(-2.28, -0.48)	(-1.82, -0.35)
LS mean difference (tofersen - placebo)		0.3
SE		0.56
95% CI		(-0.81, 1.39)
p-value		0.6025
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.46, 0.82)
p-value		0.5757

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	17 (89.5)	40 (93.0)
Number of imputed values per imputation	2 (10.5)	3 (7.0)
LS mean change from baseline	-2.2	-0.8
SE	0.62	0.50
95% CI	(-3.44, -1.02)	(-1.77, 0.20)
LS mean difference (tofersen - placebo)		1.4
SE		0.59
95% CI		(0.28, 2.61)
p-value		0.0148
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(0.03, 1.19)
p-value		0.0377

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Respiratory Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	16 (94.1)	23 (79.3)
Number of imputed values per imputation	1 (5.9)	6 (20.7)
LS mean change from baseline	-1.3	-1.8
SE	0.77	0.63
95% CI	(-2.79, 0.25)	(-3.06, -0.58)
LS mean difference (tofersen - placebo)		-0.5
SE		0.93
95% CI		(-2.37, 1.27)
p-value		0.5540
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.77, 0.51)
p-value		0.6947

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

ALSFRS-R Respiratory Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	17 (89.5)	40 (93.0)
Number of imputed values per imputation	2 (10.5)	3 (7.0)
LS mean change from baseline	-1.4	-0.9
SE	0.84	0.68
95% CI	(-3.05, 0.24)	(-2.27, 0.41)
LS mean difference (tofersen - placebo)		0.5
SE		0.82
95% CI		(-1.13, 2.08)
p-value		0.5628
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.40, 0.73)
p-value		0.5690

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-d-alsf-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Bulbar Function Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-0.5	-1.2
SE	0.51	0.39
95% CI	(-1.55, 0.47)	(-1.99, -0.46)
LS mean difference (tofersen - placebo)		-0.7
SE		0.52
95% CI		(-1.70, 0.33)
p-value		0.1842
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-1.04, 0.25)
p-value		0.2248

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Bulbar Function Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	20 (95.2)	29 (85.3)
Number of imputed values per imputation	1 (4.8)	5 (14.7)
LS mean change from baseline	-0.4	-0.3
SE	0.29	0.25
95% CI	(-0.99, 0.15)	(-0.77, 0.22)
LS mean difference (tofersen - placebo)		0.1
SE		0.36
95% CI		(-0.56, 0.84)
p-value		0.6930
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.40, 0.74)
p-value		0.5576

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-2.6	-1.9
SE	0.76	0.58
95% CI	(-4.12, -1.16)	(-3.01, -0.73)
LS mean difference (tofersen - placebo)		0.8
SE		0.76
95% CI		(-0.73, 2.27)
p-value		0.3128
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.39, 0.89)
p-value		0.4396

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	20 (95.2)	29 (85.3)
Number of imputed values per imputation	1 (4.8)	5 (14.7)
LS mean change from baseline	-1.5	-0.7
SE	0.51	0.42
95% CI	(-2.48, -0.49)	(-1.50, 0.13)
LS mean difference (tofersen - placebo)		0.8
SE		0.60
95% CI		(-0.37, 1.97)
p-value		0.1793
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.13, 1.02)
p-value		0.1289

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-2.6	-1.6
SE	0.70	0.53
95% CI	(-3.98, -1.23)	(-2.67, -0.58)
LS mean difference (tofersen - placebo)		1.0
SE		0.71
95% CI		(-0.41, 2.38)
p-value		0.1659
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.28, 1.01)
p-value		0.2695

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	20 (95.2)	29 (85.3)
Number of imputed values per imputation	1 (4.8)	5 (14.7)
LS mean change from baseline	-1.4	-0.4
SE	0.44	0.36
95% CI	(-2.25, -0.52)	(-1.15, 0.27)
LS mean difference (tofersen - placebo)		0.9
SE		0.53
95% CI		(-0.10, 2.00)
p-value		0.0765
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(0.02, 1.18)
p-value		0.0443

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Respiratory Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-2.3	-2.5
SE	1.05	0.81
95% CI	(-4.35, -0.22)	(-4.08, -0.91)
LS mean difference (tofersen - placebo)		-0.2
SE		1.09
95% CI		(-2.34, 1.91)
p-value		0.8431
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.72, 0.56)
p-value		0.8004

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Respiratory Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	20 (95.2)	29 (85.3)
Number of imputed values per imputation	1 (4.8)	5 (14.7)
LS mean change from baseline	-1.0	-0.3
SE	0.57	0.47
95% CI	(-2.08, 0.14)	(-1.23, 0.60)
LS mean difference (tofersen - placebo)		0.7
SE		0.66
95% CI		(-0.64, 1.95)
p-value		0.3238
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.29, 0.85)
p-value		0.3397

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Bulbar Function Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	19 (95.0)	30 (88.2)
Number of imputed values per imputation	1 (5.0)	4 (11.8)
LS mean change from baseline	-0.2	-0.1
SE	0.21	0.18
95% CI	(-0.64, 0.20)	(-0.45, 0.28)
LS mean difference (tofersen - placebo)		0.1
SE		0.26
95% CI		(-0.38, 0.64)
p-value		0.6097
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.44, 0.71)
p-value		0.6348

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Bulbar Function Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	14 (87.5)	33 (86.8)
Number of imputed values per imputation	2 (12.5)	5 (13.2)
LS mean change from baseline	-0.8	-1.3
SE	0.55	0.43
95% CI	(-1.91, 0.25)	(-2.17, -0.49)
LS mean difference (tofersen - placebo)		-0.5
SE		0.56
95% CI		(-1.60, 0.60)
p-value		0.3710
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.89, 0.36)
p-value		0.4100

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	19 (95.0)	30 (88.2)
Number of imputed values per imputation	1 (5.0)	4 (11.8)
LS mean change from baseline	-0.5	-0.6
SE	0.30	0.25
95% CI	(-1.12, 0.04)	(-1.06, -0.07)
LS mean difference (tofersen - placebo)		0.0
SE		0.36
95% CI		(-0.74, 0.68)
p-value		0.9347
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.40, 0.75)
p-value		0.5483

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	14 (87.5)	33 (86.8)
Number of imputed values per imputation	2 (12.5)	5 (13.2)
LS mean change from baseline	-3.8	-1.8
SE	0.76	0.59
95% CI	(-5.30, -2.31)	(-3.01, -0.68)
LS mean difference (tofersen - placebo)		2.0
SE		0.77
95% CI		(0.45, 3.47)
p-value		0.0108
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(-0.03, 1.25)
p-value		0.0598

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	19 (95.0)	30 (88.2)
Number of imputed values per imputation	1 (5.0)	4 (11.8)
LS mean change from baseline	-0.9	-0.2
SE	0.43	0.36
95% CI	(-1.77, -0.07)	(-0.94, 0.48)
LS mean difference (tofersen - placebo)		0.7
SE		0.52
95% CI		(-0.33, 1.71)
p-value		0.1858
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.05, 1.12)
p-value		0.0719

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	14 (87.5)	33 (86.8)
Number of imputed values per imputation	2 (12.5)	5 (13.2)
LS mean change from baseline	-3.1	-1.8
SE	0.60	0.46
95% CI	(-4.32, -1.97)	(-2.67, -0.85)
LS mean difference (tofersen - placebo)		1.4
SE		0.61
95% CI		(0.20, 2.57)
p-value		0.0222
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(-0.08, 1.19)
p-value		0.0859

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Respiratory Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	19 (95.0)	30 (88.2)
Number of imputed values per imputation	1 (5.0)	4 (11.8)
LS mean change from baseline	-0.1	-0.3
SE	0.39	0.33
95% CI	(-0.82, 0.72)	(-0.98, 0.31)
LS mean difference (tofersen - placebo)		-0.3
SE		0.47
95% CI		(-1.20, 0.63)
p-value		0.5398
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.73, 0.42)
p-value		0.5938

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Respiratory Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	14 (87.5)	33 (86.8)
Number of imputed values per imputation	2 (12.5)	5 (13.2)
LS mean change from baseline	-3.3	-2.4
SE	1.08	0.85
95% CI	(-5.47, -1.22)	(-4.09, -0.78)
LS mean difference (tofersen - placebo)		0.9
SE		1.11
95% CI		(-1.26, 3.09)
p-value		0.4113
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.87)
p-value		0.4429

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Bulbar Function Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	21 (95.5)	42 (93.3)
Number of imputed values per imputation	1 (4.5)	3 (6.7)
LS mean change from baseline	-0.3	-0.5
SE	0.29	0.20
95% CI	(-0.85, 0.27)	(-0.85, -0.05)
LS mean difference (tofersen - placebo)		-0.2
SE		0.35
95% CI		(-0.85, 0.54)
p-value		0.6586
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.64, 0.41)
p-value		0.6651

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Bulbar Function Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	21 (77.8)
Number of imputed values per imputation	2 (14.3)	6 (22.2)
LS mean change from baseline	-0.4	-0.6
SE	0.44	0.33
95% CI	(-1.21, 0.50)	(-1.29, -0.01)
LS mean difference (tofersen - placebo)		-0.3
SE		0.54
95% CI		(-1.36, 0.77)
p-value		0.5890
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.90, 0.52)
p-value		0.6077

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	21 (95.5)	42 (93.3)
Number of imputed values per imputation	1 (4.5)	3 (6.7)
LS mean change from baseline	-1.5	-0.9
SE	0.40	0.29
95% CI	(-2.28, -0.69)	(-1.43, -0.30)
LS mean difference (tofersen - placebo)		0.6
SE		0.50
95% CI		(-0.35, 1.59)
p-value		0.2128
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.17, 0.88)
p-value		0.1871

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	21 (77.8)
Number of imputed values per imputation	2 (14.3)	6 (22.2)
LS mean change from baseline	-2.7	-2.1
SE	0.72	0.53
95% CI	(-4.09, -1.27)	(-3.11, -1.03)
LS mean difference (tofersen - placebo)		0.6
SE		0.90
95% CI		(-1.15, 2.37)
p-value		0.4987
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.47, 0.96)
p-value		0.4976

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	21 (95.5)	42 (93.3)
Number of imputed values per imputation	1 (4.5)	3 (6.7)
LS mean change from baseline	-1.2	-0.9
SE	0.41	0.29
95% CI	(-2.01, -0.41)	(-1.44, -0.32)
LS mean difference (tofersen - placebo)		0.3
SE		0.50
95% CI		(-0.65, 1.31)
p-value		0.5106
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.31, 0.74)
p-value		0.4276

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	21 (77.8)
Number of imputed values per imputation	2 (14.3)	6 (22.2)
LS mean change from baseline	-3.1	-1.4
SE	0.56	0.42
95% CI	(-4.22, -2.04)	(-2.25, -0.61)
LS mean difference (tofersen - placebo)		1.7
SE		0.70
95% CI		(0.34, 3.07)
p-value		0.0146
Hedge's g standardized mean difference (tofersen - placebo)		0.7
95% CI		(0.01, 1.48)
p-value		0.0473

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Respiratory Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	21 (95.5)	42 (93.3)
Number of imputed values per imputation	1 (4.5)	3 (6.7)
LS mean change from baseline	-1.5	-1.4
SE	0.62	0.43
95% CI	(-2.67, -0.24)	(-2.20, -0.51)
LS mean difference (tofersen - placebo)		0.1
SE		0.76
95% CI		(-1.38, 1.58)
p-value		0.8952
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.44, 0.61)
p-value		0.7515

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

ALSFRS-R Respiratory Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	21 (77.8)
Number of imputed values per imputation	2 (14.3)	6 (22.2)
LS mean change from baseline	-1.2	-1.3
SE	0.80	0.61
95% CI	(-2.79, 0.33)	(-2.49, -0.09)
LS mean difference (tofersen - placebo)		-0.1
SE		1.00
95% CI		(-2.03, 1.91)
p-value		0.9523
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.76, 0.66)
p-value		0.8899

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, and baseline ALSFRS-R domain score. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.

Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Bulbar Function Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-0.7	-1.4
SE	0.48	0.41
95% CI	(-1.69, 0.19)	(-2.18, -0.60)
LS mean difference (tofersen - placebo)		-0.6
SE		0.48
95% CI		(-1.58, 0.30)
p-value		0.1800
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.91, 0.23)
p-value		0.2451

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Bulbar Function Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	14 (93.3)	30 (90.9)
Number of imputed values per imputation	1 (6.7)	3 (9.1)
LS mean change from baseline	-0.3	0.0
SE	0.23	0.17
95% CI	(-0.75, 0.17)	(-0.37, 0.30)
LS mean difference (tofersen - placebo)		0.3
SE		0.27
95% CI		(-0.27, 0.78)
p-value		0.3460
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.38, 0.90)
p-value		0.4256

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Fine Motor Skill Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-2.6	-1.7
SE	0.73	0.61
95% CI	(-4.07, -1.22)	(-2.88, -0.49)
LS mean difference (tofersen - placebo)		1.0
SE		0.72
95% CI		(-0.45, 2.37)
p-value		0.1816
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.18, 0.96)
p-value		0.1796

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	14 (93.3)	30 (90.9)
Number of imputed values per imputation	1 (6.7)	3 (9.1)
LS mean change from baseline	-1.0	-0.9
SE	0.44	0.32
95% CI	(-1.88, -0.17)	(-1.53, -0.27)
LS mean difference (tofersen - placebo)		0.1
SE		0.51
95% CI		(-0.87, 1.11)
p-value		0.8062
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.55, 0.72)
p-value		0.7950

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
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233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Gross Motor Skill Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-2.7	-1.6
SE	0.64	0.54
95% CI	(-3.96, -1.45)	(-2.70, -0.58)
LS mean difference (tofersen - placebo)		1.1
SE		0.63
95% CI		(-0.18, 2.30)
p-value		0.0951
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.10, 1.04)
p-value		0.1081

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	14 (93.3)	30 (90.9)
Number of imputed values per imputation	1 (6.7)	3 (9.1)
LS mean change from baseline	-0.9	-0.5
SE	0.41	0.30
95% CI	(-1.73, -0.12)	(-1.04, 0.14)
LS mean difference (tofersen - placebo)		0.5
SE		0.48
95% CI		(-0.47, 1.42)
p-value		0.3273
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.31, 0.97)
p-value		0.3092

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Respiratory Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-2.5	-2.7
SE	0.98	0.83
95% CI	(-4.38, -0.56)	(-4.36, -1.11)
LS mean difference (tofersen - placebo)		-0.3
SE		0.98
95% CI		(-2.19, 1.66)
p-value		0.7864
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.63, 0.50)
p-value		0.8165

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Respiratory Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	14 (93.3)	30 (90.9)
Number of imputed values per imputation	1 (6.7)	3 (9.1)
LS mean change from baseline	-0.3	0.0
SE	0.39	0.29
95% CI	(-1.11, 0.42)	(-0.60, 0.52)
LS mean difference (tofersen - placebo)		0.3
SE		0.45
95% CI		(-0.58, 1.18)
p-value		0.5017
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.41, 0.86)
p-value		0.4903

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Bulbar Function Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	21 (91.3)	42 (91.3)
Number of imputed values per imputation	2 (8.7)	4 (8.7)
LS mean change from baseline	-0.7	-0.7
SE	0.36	0.27
95% CI	(-1.43, -0.03)	(-1.23, -0.17)
LS mean difference (tofersen - placebo)		0.0
SE		0.38
95% CI		(-0.71, 0.78)
p-value		0.9274
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.55, 0.49)
p-value		0.9087

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Bulbar Function Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	21 (80.8)
Number of imputed values per imputation	1 (7.7)	5 (19.2)
LS mean change from baseline	0.2	-0.7
SE	0.46	0.37
95% CI	(-0.74, 1.06)	(-1.46, -0.01)
LS mean difference (tofersen - placebo)		-0.9
SE		0.52
95% CI		(-1.92, 0.13)
p-value		0.0862
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-1.06, 0.37)
p-value		0.3468

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Fine Motor Skill Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	21 (91.3)	42 (91.3)
Number of imputed values per imputation	2 (8.7)	4 (8.7)
LS mean change from baseline	-2.4	-1.2
SE	0.56	0.43
95% CI	(-3.48, -1.27)	(-2.01, -0.34)
LS mean difference (tofersen - placebo)		1.2
SE		0.60
95% CI		(0.02, 2.37)
p-value		0.0459
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.13, 0.93)
p-value		0.1373

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
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233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Fine Motor Skill Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	21 (80.8)
Number of imputed values per imputation	1 (7.7)	5 (19.2)
LS mean change from baseline	-1.2	-1.7
SE	0.68	0.54
95% CI	(-2.51, 0.15)	(-2.73, -0.63)
LS mean difference (tofersen - placebo)		-0.5
SE		0.75
95% CI		(-1.98, 0.98)
p-value		0.5056
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.61, 0.81)
p-value		0.7806

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
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233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	21 (91.3)	42 (91.3)
Number of imputed values per imputation	2 (8.7)	4 (8.7)
LS mean change from baseline	-1.9	-0.8
SE	0.54	0.41
95% CI	(-2.95, -0.85)	(-1.56, 0.05)
LS mean difference (tofersen - placebo)		1.1
SE		0.57
95% CI		(0.02, 2.27)
p-value		0.0461
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.10, 0.96)
p-value		0.1130

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
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233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Gross Motor Skill Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	21 (80.8)
Number of imputed values per imputation	1 (7.7)	5 (19.2)
LS mean change from baseline	-1.7	-1.5
SE	0.50	0.40
95% CI	(-2.66, -0.70)	(-2.29, -0.72)
LS mean difference (tofersen - placebo)		0.2
SE		0.56
95% CI		(-0.92, 1.27)
p-value		0.7558
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.29, 1.14)
p-value		0.2431

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Respiratory Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	21 (91.3)	42 (91.3)
Number of imputed values per imputation	2 (8.7)	4 (8.7)
LS mean change from baseline	-1.7	-1.0
SE	0.68	0.52
95% CI	(-3.00, -0.34)	(-1.98, 0.04)
LS mean difference (tofersen - placebo)		0.7
SE		0.72
95% CI		(-0.72, 2.12)
p-value		0.3312
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.32, 0.73)
p-value		0.4443

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: ALSFRS-R domain score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

ALSFRS-R Respiratory Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	21 (80.8)
Number of imputed values per imputation	1 (7.7)	5 (19.2)
LS mean change from baseline	-1.0	-2.2
SE	1.01	0.80
95% CI	(-2.95, 1.02)	(-3.77, -0.65)
LS mean difference (tofersen - placebo)		-1.2
SE		1.12
95% CI		(-3.45, 0.95)
p-value		0.2664
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.95, 0.48)
p-value		0.5197

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R domain score, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-anc-mi-sgrp.sas:t-cf-alsf-d-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.2232	0.2122	0.1931
Baseline disease duration since symptom onset by median	0.2603	0.2627	0.1819
Baseline NfL plasma level by median	0.6129	0.6807	0.8538
Riluzole or edaravone use	0.8706	0.8756	0.8900
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3080	0.3253	0.3896
Age at first dose (<55, >=55)	0.0697	0.0729	0.3553

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-int-itt.sas **Data Cutoff:** 16JUL2021 **Run Date:** 22JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	17.7	28.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.45
SE of log(RR)		0.581
95% CI		(0.464, 4.528)
p-value		0.5227
Adjusted OR - Odds Ratio (tofersen/placebo)		1.59
SE of log(OR)		0.737
95% CI		(0.376, 6.757)
p-value		0.5264
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.130
95% CI		(-0.148, 0.361)
p-value		0.4114

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	36.7	23.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.60
SE of log(RR)		0.426
95% CI		(0.261, 1.390)
p-value		0.2352
Adjusted OR - Odds Ratio (tofersen/placebo)		0.45
SE of log(OR)		0.689
95% CI		(0.117, 1.750)
p-value		0.2510
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.14
SE of ARR		0.134
95% CI		(-0.398, 0.127)
p-value		0.3112

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	26.5	36.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.44
SE of log(RR)		0.539
95% CI		(0.500, 4.141)
p-value		0.4994
Adjusted OR - Odds Ratio (tofersen/placebo)		1.65
SE of log(OR)		0.715
95% CI		(0.405, 6.681)
p-value		0.4862
ARR - Absolute Risk Reduction (tofersen - placebo)		0.10
SE of ARR		0.148
95% CI		(-0.193, 0.386)
p-value		0.5121

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	28.7	13.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.59
SE of log(RR)		0.581
95% CI		(0.188, 1.839)
p-value		0.3615
Adjusted OR - Odds Ratio (tofersen/placebo)		0.50
SE of log(OR)		0.775
95% CI		(0.110, 2.299)
p-value		0.3755
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.118
95% CI		(-0.388, 0.075)
p-value		0.1863

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	10.1	2.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.53
SE of log(RR)		0.987
95% CI		(0.076, 3.655)
p-value		0.5178
Adjusted OR - Odds Ratio (tofersen/placebo)		0.51
SE of log(OR)		1.095
95% CI		(0.059, 4.339)
p-value		0.5351
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.079
95% CI		(-0.230, 0.078)
p-value		0.3339

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	49.9	45.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.91
SE of log(RR)		0.401
95% CI		(0.413, 1.993)
p-value		0.8086
Adjusted OR - Odds Ratio (tofersen/placebo)		0.85
SE of log(OR)		0.622
95% CI		(0.252, 2.890)
p-value		0.7988
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.158
95% CI		(-0.352, 0.266)
p-value		0.7826

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	24.8	21.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.90
SE of log(RR)		0.472
95% CI		(0.358, 2.276)
p-value		0.8276
Adjusted OR - Odds Ratio (tofersen/placebo)		0.87
SE of log(OR)		0.640
95% CI		(0.248, 3.046)
p-value		0.8257
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.114
95% CI		(-0.257, 0.189)
p-value		0.7640

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	32.4	31.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.01
SE of log(RR)		0.504
95% CI		(0.376, 2.709)
p-value		0.9851
Adjusted OR - Odds Ratio (tofersen/placebo)		1.02
SE of log(OR)		0.767
95% CI		(0.226, 4.565)
p-value		0.9842
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.162
95% CI		(-0.324, 0.310)
p-value		0.9661

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	33.2	38.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.16
SE of log(RR)		0.403
95% CI		(0.527, 2.557)
p-value		0.7108
Adjusted OR - Odds Ratio (tofersen/placebo)		1.25
SE of log(OR)		0.591
95% CI		(0.392, 3.976)
p-value		0.7064
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.136
95% CI		(-0.215, 0.318)
p-value		0.7066

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	20.1	9.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.48
SE of log(RR)		0.757
95% CI		(0.110, 2.139)
p-value		0.3392
Adjusted OR - Odds Ratio (tofersen/placebo)		0.44
SE of log(OR)		0.888
95% CI		(0.077, 2.497)
p-value		0.3528
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.117
95% CI		(-0.333, 0.126)
p-value		0.3786

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	32.8	23.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.59
SE of log(RR)		0.416
95% CI		(0.262, 1.335)
p-value		0.2059
Adjusted OR - Odds Ratio (tofersen/placebo)		0.47
SE of log(OR)		0.619
95% CI		(0.140, 1.586)
p-value		0.2247
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.119
95% CI		(-0.322, 0.145)
p-value		0.4580

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	18.9	27.7
Adjusted RR - Relative Risk (tofersen/placebo)		2.57
SE of log(RR)		0.700
95% CI		(0.652, 10.143)
p-value		0.1770
Adjusted OR - Odds Ratio (tofersen/placebo)		4.04
SE of log(OR)		1.032
95% CI		(0.534, 30.540)
p-value		0.1760
ARR - Absolute Risk Reduction (tofersen - placebo)		0.09
SE of ARR		0.149
95% CI		(-0.205, 0.379)
p-value		0.5578

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-wk28-sgrp.sas:t-cf-als-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Bulbar Function Domain Score

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	NA	NA	NA
Baseline disease duration since symptom onset by median	NA	NA	NA
Baseline NfL plasma level by median	0.3517	0.3786	0.7729
Riluzole or edaravone use	0.8472	0.8567	0.8805
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1792	0.1758	0.3167
Age at first dose (<55, >=55)	0.0460	0.0380	0.1189

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06JUL2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Fine Motor Skill Domain Score

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.7927	0.9994	0.9818
Baseline disease duration since symptom onset by median	0.6791	0.7807	0.5849
Baseline NfL plasma level by median	0.7510	0.7874	0.7844
Riluzole or edaravone use	0.2183	0.2703	0.3219
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.8311	0.6129	0.5456
Age at first dose (<55, >=55)	0.1842	0.2263	0.9306

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06JUL2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Gross Motor Skill Domain Score

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.3080	0.2595	0.2828
Baseline disease duration since symptom onset by median	0.6209	0.6163	0.4403
Baseline NfL plasma level by median	0.4428	0.5061	0.4709
Riluzole or edaravone use	0.3963	0.3370	0.3143
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.5636	0.6226	0.6873
Age at first dose (<55, >=55)	0.0709	0.0788	0.6173

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06JUL2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSFRS-R Respiratory Domain Score

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.4045	0.4211	0.2925
Baseline disease duration since symptom onset by median	0.3815	0.3768	0.2262
Baseline NfL plasma level by median	0.3035	0.3149	0.5375
Riluzole or edaravone use	0.4889	0.4341	0.4955
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.2996	0.2437	0.1846
Age at first dose (<55, >=55)	0.0769	0.0656	0.4606

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 06JUL2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	41.7	28.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.65
SE of log(RR)		0.386
95% CI		(0.304, 1.384)
p-value		0.2632
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.681
95% CI		(0.130, 1.880)
p-value		0.3015
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.151
95% CI		(-0.426, 0.167)
p-value		0.3927

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	52.5	40.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.270
95% CI		(0.433, 1.246)
p-value		0.2525
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.645
95% CI		(0.140, 1.748)
p-value		0.2742
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.137
95% CI		(-0.394, 0.145)
p-value		0.3639

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	35.5	40.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.10
SE of log(RR)		0.407
95% CI		(0.497, 2.447)
p-value		0.8110
Adjusted OR - Odds Ratio (tofersen/placebo)		1.16
SE of log(OR)		0.617
95% CI		(0.346, 3.882)
p-value		0.8106
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.151
95% CI		(-0.245, 0.347)
p-value		0.7351

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	52.2	35.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.65
SE of log(RR)		0.309
95% CI		(0.357, 1.200)
p-value		0.1704
Adjusted OR - Odds Ratio (tofersen/placebo)		0.43
SE of log(OR)		0.632
95% CI		(0.124, 1.478)
p-value		0.1794
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.17
SE of ARR		0.137
95% CI		(-0.438, 0.101)
p-value		0.2206

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Respiratory Domain Score/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	17.7	32.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.64
SE of log(RR)		0.563
95% CI		(0.545, 4.950)
p-value		0.3776
Adjusted OR - Odds Ratio (tofersen/placebo)		1.95
SE of log(OR)		0.746
95% CI		(0.451, 8.420)
p-value		0.3710
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.131
95% CI		(-0.105, 0.409)
p-value		0.2460

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
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NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by gender - ITT population

ALSFRS-R Respiratory Domain Score/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	31.6	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.92
SE of log(RR)		0.415
95% CI		(0.406, 2.068)
p-value		0.8339
Adjusted OR - Odds Ratio (tofersen/placebo)		0.86
SE of log(OR)		0.682
95% CI		(0.227, 3.289)
p-value		0.8296
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.129
95% CI		(-0.296, 0.212)
p-value		0.7463

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	53.2	45.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.84
SE of log(RR)		0.301
95% CI		(0.466, 1.516)
p-value		0.5629
Adjusted OR - Odds Ratio (tofersen/placebo)		0.70
SE of log(OR)		0.646
95% CI		(0.197, 2.471)
p-value		0.5762
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.153
95% CI		(-0.377, 0.222)
p-value		0.6124

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
ALSFRS-R is used.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	43.3	24.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.68
SE of log(RR)		0.410
95% CI		(0.305, 1.520)
p-value		0.3479
Adjusted OR - Odds Ratio (tofersen/placebo)		0.54
SE of log(OR)		0.660
95% CI		(0.148, 1.965)
p-value		0.3490
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.19
SE of ARR		0.135
95% CI		(-0.454, 0.076)
p-value		0.1616

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
ALSFRS-R is used.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	46.2	46.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.99
SE of log(RR)		0.354
95% CI		(0.497, 1.990)
p-value		0.9876
Adjusted OR - Odds Ratio (tofersen/placebo)		1.00
SE of log(OR)		0.600
95% CI		(0.307, 3.229)
p-value		0.9936
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.154
95% CI		(-0.300, 0.306)
p-value		0.9838

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
ALSFRS-R is used.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	43.0	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.78
SE of log(RR)		0.354
95% CI		(0.388, 1.552)
p-value		0.4735
Adjusted OR - Odds Ratio (tofersen/placebo)		0.64
SE of log(OR)		0.647
95% CI		(0.180, 2.270)
p-value		0.4886
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.135
95% CI		(-0.421, 0.110)
p-value		0.2500

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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ALSFRS-R is used.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Respiratory Domain Score/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	26.8	41.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.75
SE of log(RR)		0.489
95% CI		(0.670, 4.553)
p-value		0.2537
Adjusted OR - Odds Ratio (tofersen/placebo)		2.35
SE of log(OR)		0.693
95% CI		(0.603, 9.130)
p-value		0.2183
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.144
95% CI		(-0.133, 0.431)
p-value		0.3016

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ALSFRS-R is used.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSFRS-R Respiratory Domain Score/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	23.8	16.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.93
SE of log(RR)		0.519
95% CI		(0.338, 2.582)
p-value		0.8952
Adjusted OR - Odds Ratio (tofersen/placebo)		0.92
SE of log(OR)		0.799
95% CI		(0.192, 4.397)
p-value		0.9145
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.116
95% CI		(-0.303, 0.152)
p-value		0.5143

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
ALSFRS-R is used.
NOTE 5: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSFRS-R Bulbar Function Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	10.0	3.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.44
SE of log(RR)		1.017
95% CI		(0.060, 3.220)
p-value		0.4175
Adjusted OR - Odds Ratio (tofersen/placebo)		0.38
SE of log(OR)		1.292
95% CI		(0.030, 4.759)
p-value		0.4515
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.076
95% CI		(-0.211, 0.089)
p-value		0.4232

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Bulbar Function Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	25.4	23.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.26
SE of log(RR)		0.509
95% CI		(0.465, 3.422)
p-value		0.6483
Adjusted OR - Odds Ratio (tofersen/placebo)		1.40
SE of log(OR)		0.736
95% CI		(0.330, 5.913)
p-value		0.6506
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.131
95% CI		(-0.274, 0.239)
p-value		0.8933

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Fine Motor Skill Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	25.5	12.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.55
SE of log(RR)		0.719
95% CI		(0.134, 2.239)
p-value		0.4015
Adjusted OR - Odds Ratio (tofersen/placebo)		0.51
SE of log(OR)		0.793
95% CI		(0.107, 2.394)
p-value		0.3897
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.116
95% CI		(-0.362, 0.093)
p-value		0.2474

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSFRS-R Fine Motor Skill Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	74.9	56.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.70
SE of log(RR)		0.246
95% CI		(0.430, 1.127)
p-value		0.1402
Adjusted OR - Odds Ratio (tofersen/placebo)		0.38
SE of log(OR)		0.684
95% CI		(0.100, 1.455)
p-value		0.1583
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.18
SE of ARR		0.136
95% CI		(-0.451, 0.084)
p-value		0.1788

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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	30.2	13.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.53
SE of log(RR)		0.625
95% CI		(0.157, 1.812)
p-value		0.3132
Adjusted OR - Odds Ratio (tofersen/placebo)		0.43
SE of log(OR)		0.780
95% CI		(0.094, 2.004)
p-value		0.2851
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.17
SE of ARR		0.120
95% CI		(-0.403, 0.069)
p-value		0.1643

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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSFRS-R Gross Motor Skill Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	62.0	59.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.91
SE of log(RR)		0.305
95% CI		(0.499, 1.649)
p-value		0.7490
Adjusted OR - Odds Ratio (tofersen/placebo)		0.83
SE of log(OR)		0.585
95% CI		(0.264, 2.613)
p-value		0.7498
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.148
95% CI		(-0.320, 0.260)
p-value		0.8391

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NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Respiratory Domain Score/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	5.1	11.5
Adjusted RR - Relative Risk (tofersen/placebo)		3.13
SE of log(RR)		1.014
95% CI		(0.429, 22.862)
p-value		0.2601
Adjusted OR - Odds Ratio (tofersen/placebo)		4.53
SE of log(OR)		1.313
95% CI		(0.346, 59.372)
p-value		0.2497
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.077
95% CI		(-0.086, 0.214)
p-value		0.4023

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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSFRS-R Respiratory Domain Score/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	50.1	45.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.367
95% CI		(0.503, 2.118)
p-value		0.9315
Adjusted OR - Odds Ratio (tofersen/placebo)		1.05
SE of log(OR)		0.613
95% CI		(0.317, 3.509)
p-value		0.9306
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.153
95% CI		(-0.341, 0.259)
p-value		0.7867

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
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NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSFRS-R Bulbar Function Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	18.3	14.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.83
SE of log(RR)		0.580
95% CI		(0.266, 2.583)
p-value		0.7469
Adjusted OR - Odds Ratio (tofersen/placebo)		0.80
SE of log(OR)		0.691
95% CI		(0.207, 3.111)
p-value		0.7501
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.099
95% CI		(-0.228, 0.159)
p-value		0.7272

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Bulbar Function Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	14.6	13.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.00
SE of log(RR)		0.791
95% CI		(0.213, 4.720)
p-value		0.9978
Adjusted OR - Odds Ratio (tofersen/placebo)		1.01
SE of log(OR)		1.059
95% CI		(0.126, 8.045)
p-value		0.9935
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.119
95% CI		(-0.244, 0.221)
p-value		0.9243

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
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Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	45.5	25.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.59
SE of log(RR)		0.331
95% CI		(0.307, 1.123)
p-value		0.1075
Adjusted OR - Odds Ratio (tofersen/placebo)		0.41
SE of log(OR)		0.583
95% CI		(0.130, 1.280)
p-value		0.1242
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.20
SE of ARR		0.125
95% CI		(-0.443, 0.049)
p-value		0.1167

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	50.5	51.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.05
SE of log(RR)		0.337
95% CI		(0.542, 2.029)
p-value		0.8873
Adjusted OR - Odds Ratio (tofersen/placebo)		1.11
SE of log(OR)		0.700
95% CI		(0.282, 4.385)
p-value		0.8795
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.170
95% CI		(-0.321, 0.345)
p-value		0.9435

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	31.8	33.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.07
SE of log(RR)		0.376
95% CI		(0.514, 2.240)
p-value		0.8521
Adjusted OR - Odds Ratio (tofersen/placebo)		1.11
SE of log(OR)		0.555
95% CI		(0.374, 3.292)
p-value		0.8514
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.122
95% CI		(-0.226, 0.254)
p-value		0.9086

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	63.9	44.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.71
SE of log(RR)		0.313
95% CI		(0.383, 1.308)
p-value		0.2704
Adjusted OR - Odds Ratio (tofersen/placebo)		0.47
SE of log(OR)		0.715
95% CI		(0.115, 1.888)
p-value		0.2841
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.19
SE of ARR		0.166
95% CI		(-0.519, 0.132)
p-value		0.2434

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSFRS-R Respiratory Domain Score/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	26.5	26.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.429
95% CI		(0.445, 2.398)
p-value		0.9391
Adjusted OR - Odds Ratio (tofersen/placebo)		1.05
SE of log(OR)		0.613
95% CI		(0.314, 3.477)
p-value		0.9418
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.117
95% CI		(-0.232, 0.226)
p-value		0.9780

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSFRS-R Respiratory Domain Score/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	22.8	35.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.67
SE of log(RR)		0.540
95% CI		(0.578, 4.810)
p-value		0.3438
Adjusted OR - Odds Ratio (tofersen/placebo)		2.44
SE of log(OR)		0.889
95% CI		(0.427, 13.916)
p-value		0.3165
ARR - Absolute Risk Reduction (tofersen - placebo)		0.13
SE of ARR		0.150
95% CI		(-0.168, 0.421)
p-value		0.3991

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Bulbar Function Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	19.3	23.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.23
SE of log(RR)		0.552
95% CI		(0.416, 3.621)
p-value		0.7097
Adjusted OR - Odds Ratio (tofersen/placebo)		1.29
SE of log(OR)		0.668
95% CI		(0.348, 4.776)
p-value		0.7034
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.112
95% CI		(-0.176, 0.264)
p-value		0.6944

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Bulbar Function Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	13.3	3.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.22
SE of log(RR)		1.138
95% CI		(0.024, 2.095)
p-value		0.1900
Adjusted OR - Odds Ratio (tofersen/placebo)		0.17
SE of log(OR)		1.331
95% CI		(0.013, 2.338)
p-value		0.1863
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.093
95% CI		(-0.284, 0.081)
p-value		0.2740

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Fine Motor Skill Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	61.8	46.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.75
SE of log(RR)		0.245
95% CI		(0.463, 1.208)
p-value		0.2346
Adjusted OR - Odds Ratio (tofersen/placebo)		0.52
SE of log(OR)		0.572
95% CI		(0.169, 1.595)
p-value		0.2525
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.135
95% CI		(-0.422, 0.106)
p-value		0.2396

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Fine Motor Skill Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	27.3	23.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.85
SE of log(RR)		0.566
95% CI		(0.281, 2.583)
p-value		0.7777
Adjusted OR - Odds Ratio (tofersen/placebo)		0.82
SE of log(OR)		0.702
95% CI		(0.207, 3.245)
p-value		0.7779
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.139
95% CI		(-0.315, 0.232)
p-value		0.7662

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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Gross Motor Skill Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	52.0	49.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.96
SE of log(RR)		0.281
95% CI		(0.553, 1.665)
p-value		0.8822
Adjusted OR - Odds Ratio (tofersen/placebo)		0.93
SE of log(OR)		0.539
95% CI		(0.322, 2.665)
p-value		0.8882
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.138
95% CI		(-0.294, 0.246)
p-value		0.8626

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NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Gross Motor Skill Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	33.5	23.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.69
SE of log(RR)		0.497
95% CI		(0.260, 1.827)
p-value		0.4549
Adjusted OR - Odds Ratio (tofersen/placebo)		0.60
SE of log(OR)		0.697
95% CI		(0.153, 2.357)
p-value		0.4650
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.144
95% CI		(-0.387, 0.178)
p-value		0.4701

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Respiratory Domain Score/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	33.4	49.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.47
SE of log(RR)		0.366
95% CI		(0.720, 3.017)
p-value		0.2886
Adjusted OR - Odds Ratio (tofersen/placebo)		1.90
SE of log(OR)		0.571
95% CI		(0.619, 5.805)
p-value		0.2630
ARR - Absolute Risk Reduction (tofersen - placebo)		0.16
SE of ARR		0.134
95% CI		(-0.107, 0.419)
p-value		0.2454

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NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSFRS-R Respiratory Domain Score/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	13.4	6.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.50
SE of log(RR)		0.982
95% CI		(0.073, 3.409)
p-value		0.4773
Adjusted OR - Odds Ratio (tofersen/placebo)		0.50
SE of log(OR)		1.001
95% CI		(0.070, 3.523)
p-value		0.4827
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.100
95% CI		(-0.261, 0.130)
p-value		0.5091

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
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233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Bulbar Function Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	21.9	10.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.32
SE of log(RR)		0.662
95% CI		(0.088, 1.181)
p-value		0.0875
Adjusted OR - Odds Ratio (tofersen/placebo)		0.25
SE of log(OR)		0.808
95% CI		(0.051, 1.204)
p-value		0.0836
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.098
95% CI		(-0.302, 0.082)
p-value		0.2624

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Bulbar Function Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	7.9	20.4
Adjusted RR - Relative Risk (tofersen/placebo)		4.97
SE of log(RR)		1.199
95% CI		(0.474, 52.063)
p-value		0.1812
Adjusted OR - Odds Ratio (tofersen/placebo)		9.02
SE of log(OR)		1.536
95% CI		(0.443, 183.359)
p-value		0.1524
ARR - Absolute Risk Reduction (tofersen - placebo)		0.12
SE of ARR		0.114
95% CI		(-0.099, 0.348)
p-value		0.2742

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Fine Motor Skill Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	48.1	35.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.67
SE of log(RR)		0.288
95% CI		(0.383, 1.183)
p-value		0.1690
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.560
95% CI		(0.163, 1.461)
p-value		0.1996
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.127
95% CI		(-0.375, 0.124)
p-value		0.3226

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Fine Motor Skill Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	46.2	35.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.28
SE of log(RR)		0.387
95% CI		(0.597, 2.727)
p-value		0.5291
Adjusted OR - Odds Ratio (tofersen/placebo)		1.88
SE of log(OR)		0.968
95% CI		(0.282, 12.558)
p-value		0.5134
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.171
95% CI		(-0.443, 0.228)
p-value		0.5307

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Gross Motor Skill Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	43.3	32.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.332
95% CI		(0.342, 1.257)
p-value		0.2039
Adjusted OR - Odds Ratio (tofersen/placebo)		0.51
SE of log(OR)		0.554
95% CI		(0.172, 1.512)
p-value		0.2248
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.126
95% CI		(-0.354, 0.140)
p-value		0.3962

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Gross Motor Skill Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	46.2	46.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.66
SE of log(RR)		0.391
95% CI		(0.771, 3.571)
p-value		0.1958
Adjusted OR - Odds Ratio (tofersen/placebo)		4.03
SE of log(OR)		1.035
95% CI		(0.531, 30.661)
p-value		0.1776
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.173
95% CI		(-0.339, 0.339)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Respiratory Domain Score/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	26.9	26.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.424
95% CI		(0.320, 1.688)
p-value		0.4684
Adjusted OR - Odds Ratio (tofersen/placebo)		0.62
SE of log(OR)		0.669
95% CI		(0.167, 2.306)
p-value		0.4767
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.115
95% CI		(-0.231, 0.220)
p-value		0.9623

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSFRS-R Respiratory Domain Score/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	21.8	35.5
Adjusted RR - Relative Risk (tofersen/placebo)		2.70
SE of log(RR)		0.597
95% CI		(0.838, 8.688)
p-value		0.0963
Adjusted OR - Odds Ratio (tofersen/placebo)		5.83
SE of log(OR)		1.007
95% CI		(0.810, 41.990)
p-value		0.0799
ARR - Absolute Risk Reduction (tofersen - placebo)		0.14
SE of ARR		0.154
95% CI		(-0.166, 0.439)
p-value		0.3751

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-wor-d-wk28-sgrp.sas:t-cf-als-wor-d-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29JUN2023

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R total score >=15% at Week 28 using MI: treatment by subgroup interaction – ITT population

Subgroup analyses not performed. Condition of having at least 10 events in at least one of the subgroup categories for binary endpoint is not met.

233AS101 Part C: Summary of proportion of improvement in ALSFRS-R domain score >=15% at Week 28 using MI: treatment by subgroup interaction – ITT population

Subgroup analyses not performed. Condition of having at least 10 events in at least one of the subgroup categories for binary endpoint is not met.

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.0217
Baseline disease duration since symptom onset by median	0.1636
Baseline NfL plasma level by median	0.7206
Riluzole or edaravone use	0.3716
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.7731
Age at first dose (<55, >=55)	0.2475

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline HHD overall megascore, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 01JUN2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	14 (82.4)	21 (72.4)
Number of imputed values per imputation	3 (17.6)	8 (27.6)
LS mean change from baseline	-0.1	-0.3
SE	0.07	0.06
95% CI	(-0.26, 0.02)	(-0.39, -0.15)
LS mean difference (tofersen - placebo)		-0.2
SE		0.09
95% CI		(-0.33, 0.03)
p-value		0.1033
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.94, 0.42)
p-value		0.4465

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	13 (68.4)	37 (86.0)
Number of imputed values per imputation	6 (31.6)	6 (14.0)
LS mean change from baseline	-0.4	-0.2
SE	0.12	0.10
95% CI	(-0.61, -0.14)	(-0.34, 0.03)
LS mean difference (tofersen - placebo)		0.2
SE		0.12
95% CI		(-0.01, 0.45)
p-value		0.0592
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.14, 1.14)
p-value		0.1269

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	11 (73.3)	33 (86.8)
Number of imputed values per imputation	4 (26.7)	5 (13.2)
LS mean change from baseline	-0.4	-0.4
SE	0.13	0.10
95% CI	(-0.63, -0.11)	(-0.59, -0.20)
LS mean difference (tofersen - placebo)		0.0
SE		0.13
95% CI		(-0.29, 0.23)
p-value		0.8304
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.82, 0.55)
p-value		0.7020

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	16 (76.2)	25 (73.5)
Number of imputed values per imputation	5 (23.8)	9 (26.5)
LS mean change from baseline	-0.3	-0.1
SE	0.07	0.06
95% CI	(-0.39, -0.13)	(-0.17, 0.05)
LS mean difference (tofersen - placebo)		0.2
SE		0.08
95% CI		(0.04, 0.36)
p-value		0.0130
Hedge's g standardized mean difference (tofersen - placebo)		0.8
95% CI		(0.13, 1.43)
p-value		0.0187

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	17 (85.0)	27 (79.4)
Number of imputed values per imputation	3 (15.0)	7 (20.6)
LS mean change from baseline	-0.2	-0.1
SE	0.08	0.07
95% CI	(-0.32, -0.02)	(-0.21, 0.04)
LS mean difference (tofersen - placebo)		0.1
SE		0.09
95% CI		(-0.09, 0.27)
p-value		0.3508
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.28, 0.94)
p-value		0.2902

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	10 (62.5)	31 (81.6)
Number of imputed values per imputation	6 (37.5)	7 (18.4)
LS mean change from baseline	-0.5	-0.4
SE	0.12	0.09
95% CI	(-0.73, -0.26)	(-0.53, -0.18)
LS mean difference (tofersen - placebo)		0.1
SE		0.12
95% CI		(-0.10, 0.37)
p-value		0.2690
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.53, 0.90)
p-value		0.6069

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	16 (72.7)	39 (86.7)
Number of imputed values per imputation	6 (27.3)	6 (13.3)
LS mean change from baseline	-0.2	-0.2
SE	0.08	0.05
95% CI	(-0.37, -0.06)	(-0.32, -0.12)
LS mean difference (tofersen - placebo)		0.0
SE		0.09
95% CI		(-0.19, 0.18)
p-value		0.9628
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.50, 0.66)
p-value		0.7857

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	11 (78.6)	19 (70.4)
Number of imputed values per imputation	3 (21.4)	8 (29.6)
LS mean change from baseline	-0.4	-0.3
SE	0.11	0.08
95% CI	(-0.60, -0.19)	(-0.41, -0.09)
LS mean difference (tofersen - placebo)		0.1
SE		0.13
95% CI		(-0.11, 0.40)
p-value		0.2658
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.40, 1.09)
p-value		0.3642

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	16 (76.2)	32 (82.1)
Number of imputed values per imputation	5 (23.8)	7 (17.9)
LS mean change from baseline	-0.4	-0.4
SE	0.12	0.10
95% CI	(-0.64, -0.17)	(-0.57, -0.19)
LS mean difference (tofersen - placebo)		0.0
SE		0.12
95% CI		(-0.21, 0.26)
p-value		0.8382
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.52, 0.68)
p-value		0.7895

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	11 (73.3)	26 (78.8)
Number of imputed values per imputation	4 (26.7)	7 (21.2)
LS mean change from baseline	-0.2	-0.1
SE	0.07	0.05
95% CI	(-0.32, -0.04)	(-0.19, 0.02)
LS mean difference (tofersen - placebo)		0.1
SE		0.08
95% CI		(-0.07, 0.26)
p-value		0.2832
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.33, 1.10)
p-value		0.2889

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	16 (69.6)	39 (84.8)
Number of imputed values per imputation	7 (30.4)	7 (15.2)
LS mean change from baseline	-0.4	-0.2
SE	0.10	0.07
95% CI	(-0.54, -0.17)	(-0.37, -0.09)
LS mean difference (tofersen - placebo)		0.1
SE		0.10
95% CI		(-0.07, 0.33)
p-value		0.2164
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.33, 0.84)
p-value		0.3850

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: HHD overall megascore change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	11 (84.6)	19 (73.1)
Number of imputed values per imputation	2 (15.4)	7 (26.9)
LS mean change from baseline	-0.2	-0.2
SE	0.11	0.09
95% CI	(-0.39, 0.05)	(-0.41, -0.06)
LS mean difference (tofersen - placebo)		-0.1
SE		0.13
95% CI		(-0.31, 0.18)
p-value		0.5976
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.69, 0.79)
p-value		0.8964

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A higher score or a positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline HHD overall megascore, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: HHD = handheld dynamometry; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-anc-mi-sgrp.sas:t-cf-mega-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 05MAY2023

233AS101 Part C: Percent predicted SVC change from baseline at week 28 ANCOVA analysis using MI: tretament by subgroup interaction

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Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.5060
Baseline disease duration since symptom onset by median	0.5595
Baseline NfL plasma level by median	0.5541
Riluzole or edaravone use	0.1695
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.6610
Age at first dose (<55, >=55)	0.9263

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including baseline plasma NfL, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS-R total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 01JUN2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	13 (76.5)	17 (58.6)
Number of imputed values per imputation	4 (23.5)	12 (41.4)
LS mean change from baseline	-14.3	-9.7
SE	5.08	4.08
95% CI	(-24.22, -4.32)	(-17.66, -1.67)
LS mean difference (tofersen - placebo)		4.6
SE		6.05
95% CI		(-7.25, 16.46)
p-value		0.4464
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.58, 0.87)
p-value		0.6998

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	12 (63.2)	35 (81.4)
Number of imputed values per imputation	7 (36.8)	8 (18.6)
LS mean change from baseline	-14.3	-5.0
SE	4.60	3.61
95% CI	(-23.29, -5.24)	(-12.06, 2.09)
LS mean difference (tofersen - placebo)		9.3
SE		4.50
95% CI		(0.46, 18.09)
p-value		0.0392
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(-0.07, 1.26)
p-value		0.0797

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	10 (66.7)	30 (78.9)
Number of imputed values per imputation	5 (33.3)	8 (21.1)
LS mean change from baseline	-24.2	-14.8
SE	6.42	4.97
95% CI	(-36.81, -11.63)	(-24.51, -5.04)
LS mean difference (tofersen - placebo)		9.4
SE		6.65
95% CI		(-3.58, 22.48)
p-value		0.1552
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.23, 1.22)
p-value		0.1826

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	15 (71.4)	22 (64.7)
Number of imputed values per imputation	6 (28.6)	12 (35.3)
LS mean change from baseline	-8.3	-1.9
SE	3.18	2.51
95% CI	(-14.58, -2.09)	(-6.81, 3.01)
LS mean difference (tofersen - placebo)		6.4
SE		3.77
95% CI		(-0.96, 13.83)
p-value		0.0880
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.26, 1.07)
p-value		0.2278

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	17 (85.0)	25 (73.5)
Number of imputed values per imputation	3 (15.0)	9 (26.5)
LS mean change from baseline	-5.6	0.4
SE	2.80	2.35
95% CI	(-11.11, -0.12)	(-4.17, 5.05)
LS mean difference (tofersen - placebo)		6.1
SE		3.38
95% CI		(-0.58, 12.68)
p-value		0.0736
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.12, 1.13)
p-value		0.1121

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	8 (50.0)	27 (71.1)
Number of imputed values per imputation	8 (50.0)	11 (28.9)
LS mean change from baseline	-26.1	-16.2
SE	6.15	4.68
95% CI	(-38.19, -14.07)	(-25.39, -7.05)
LS mean difference (tofersen - placebo)		9.9
SE		6.21
95% CI		(-2.27, 22.09)
p-value		0.1108
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.28, 1.31)
p-value		0.2064

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	14 (66.7)	28 (71.8)
Number of imputed values per imputation	7 (33.3)	11 (28.2)
LS mean change from baseline	-24.2	-16.3
SE	5.90	4.94
95% CI	(-35.79, -12.64)	(-26.03, -6.66)
LS mean difference (tofersen - placebo)		7.9
SE		5.84
95% CI		(-3.57, 19.31)
p-value		0.1776
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.28, 1.02)
p-value		0.2601

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	11 (73.3)	24 (72.7)
Number of imputed values per imputation	4 (26.7)	9 (27.3)
LS mean change from baseline	-4.9	-0.3
SE	2.57	1.87
95% CI	(-9.93, 0.14)	(-3.93, 3.41)
LS mean difference (tofersen - placebo)		4.6
SE		2.99
95% CI		(-1.22, 10.49)
p-value		0.1210
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.32, 1.12)
p-value		0.2764

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	16 (72.7)	35 (77.8)
Number of imputed values per imputation	6 (27.3)	10 (22.2)
LS mean change from baseline	-11.0	-8.1
SE	3.31	2.34
95% CI	(-17.50, -4.53)	(-12.67, -3.49)
LS mean difference (tofersen - placebo)		2.9
SE		4.03
95% CI		(-4.97, 10.83)
p-value		0.4672
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.81)
p-value		0.4786

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	9 (64.3)	17 (63.0)
Number of imputed values per imputation	5 (35.7)	10 (37.0)
LS mean change from baseline	-21.0	-7.7
SE	5.41	3.73
95% CI	(-31.61, -10.42)	(-15.04, -0.43)
LS mean difference (tofersen - placebo)		13.3
SE		6.58
95% CI		(0.39, 26.18)
p-value		0.0435
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(-0.27, 1.38)
p-value		0.1859

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	15 (65.2)	38 (82.6)
Number of imputed values per imputation	8 (34.8)	8 (17.4)
LS mean change from baseline	-13.7	-6.2
SE	3.89	2.88
95% CI	(-21.35, -6.09)	(-11.82, -0.55)
LS mean difference (tofersen - placebo)		7.5
SE		4.17
95% CI		(-0.64, 15.71)
p-value		0.0708
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.33, 0.87)
p-value		0.3844

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: Percent predicted SVC (percent) change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	10 (76.9)	14 (53.8)
Number of imputed values per imputation	3 (23.1)	12 (46.2)
LS mean change from baseline	-19.1	-11.3
SE	6.16	4.85
95% CI	(-31.23, -7.07)	(-20.76, -1.75)
LS mean difference (tofersen - placebo)		7.9
SE		6.80
95% CI		(-5.43, 21.21)
p-value		0.2454
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.28, 1.37)
p-value		0.1984

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A higher score or a positive change indicates an improvement.
NOTE 4: The maximum (best effort) acceptable reading is used for analysis. Readings with ATS Best criteria F (failed) are considered as missing and not included in the summary.
NOTE 5: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline percent predicted SVC, baseline ALSFRS, and use of riluzole or edaravone. Nominal p-value is presented. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SVC = slow vital capacity; ANCOVA = analysis of covariance; MI = multiple imputatio; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-anc-mi-sgrp.sas:t-cf-svc-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 16MAY2023

233AS101 Part C: EQ-5D-5L VAS change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.4830
Baseline disease duration since symptom onset by median	0.6096
Baseline NfL plasma level by median	0.1900
Riluzole or edaravone use	0.3322
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.4373
Age at first dose (<55, >=55)	0.7300

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: EQ-5D-5L VAS change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	23 (79.3)
Number of imputed values per imputation	2 (11.8)	6 (20.7)
LS mean change from baseline	-10.8	-9.1
SE	4.45	3.59
95% CI	(-19.54, -2.08)	(-16.12, -2.04)
LS mean difference (tofersen - placebo)		1.7
SE		5.35
95% CI		(-8.76, 12.22)
p-value		0.7465
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.46, 0.84)
p-value		0.5682

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	16 (84.2)	38 (88.4)
Number of imputed values per imputation	3 (15.8)	5 (11.6)
LS mean change from baseline	-11.6	-5.0
SE	5.83	4.66
95% CI	(-23.08, -0.22)	(-14.14, 4.12)
LS mean difference (tofersen - placebo)		6.6
SE		5.63
95% CI		(-4.40, 17.68)
p-value		0.2382
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.19, 0.99)
p-value		0.1828

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-15.9	-13.3
SE	5.91	4.51
95% CI	(-27.49, -4.32)	(-22.13, -4.46)
LS mean difference (tofersen - placebo)		2.6
SE		5.94
95% CI		(-9.04, 14.25)
p-value		0.6610
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.49, 0.79)
p-value		0.6440

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (85.7)	27 (79.4)
Number of imputed values per imputation	3 (14.3)	7 (20.6)
LS mean change from baseline	-9.3	-3.6
SE	4.57	3.72
95% CI	(-18.27, -0.37)	(-10.90, 3.67)
LS mean difference (tofersen - placebo)		5.7
SE		5.43
95% CI		(-4.94, 16.35)
p-value		0.2935
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.12, 1.10)
p-value		0.1125

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	-2.5	-0.9
SE	2.85	2.40
95% CI	(-8.05, 3.11)	(-5.59, 3.84)
LS mean difference (tofersen - placebo)		1.6
SE		3.43
95% CI		(-5.13, 8.32)
p-value		0.6424
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.36, 0.82)
p-value		0.4459

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (81.3)	32 (84.2)
Number of imputed values per imputation	3 (18.8)	6 (15.8)
LS mean change from baseline	-23.9	-14.1
SE	6.54	4.94
95% CI	(-36.70, -11.06)	(-23.76, -4.42)
LS mean difference (tofersen - placebo)		9.8
SE		6.54
95% CI		(-3.03, 22.60)
p-value		0.1343
Hedge's g standardized mean difference (tofersen - placebo)		0.6
95% CI		(-0.09, 1.23)
p-value		0.0888

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	42 (93.3)
Number of imputed values per imputation	3 (13.6)	3 (6.7)
LS mean change from baseline	-8.8	-7.8
SE	4.20	2.86
95% CI	(-17.04, -0.59)	(-13.42, -2.19)
LS mean difference (tofersen - placebo)		1.0
SE		5.20
95% CI		(-9.19, 11.20)
p-value		0.8467
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.31, 0.77)
p-value		0.4045

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline EQ-5D-5L VAS score. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	19 (70.4)
Number of imputed values per imputation	2 (14.3)	8 (29.6)
LS mean change from baseline	-14.6	-5.7
SE	4.98	3.69
95% CI	(-24.39, -4.85)	(-12.95, 1.52)
LS mean difference (tofersen - placebo)		8.9
SE		6.18
95% CI		(-3.20, 21.02)
p-value		0.1494
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.31, 1.16)
p-value		0.2541

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline EQ-5D-5L VAS score. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-18.0	-12.9
SE	5.75	4.69
95% CI	(-29.23, -6.69)	(-22.11, -3.71)
LS mean difference (tofersen - placebo)		5.1
SE		5.70
95% CI		(-6.12, 16.22)
p-value		0.3753
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.16, 0.98)
p-value		0.1544

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	-4.2	-3.5
SE	4.36	3.17
95% CI	(-12.75, 4.33)	(-9.68, 2.74)
LS mean difference (tofersen - placebo)		0.7
SE		5.00
95% CI		(-9.06, 10.55)
p-value		0.8818
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.58, 0.77)
p-value		0.7858

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	-11.6	-6.5
SE	4.41	3.28
95% CI	(-20.22, -2.93)	(-12.91, -0.07)
LS mean difference (tofersen - placebo)		5.1
SE		4.70
95% CI		(-4.12, 14.29)
p-value		0.2785
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.23, 0.86)
p-value		0.2616

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: EQ-5D-5L VAS score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	20 (76.9)
Number of imputed values per imputation	1 (7.7)	6 (23.1)
LS mean change from baseline	-11.3	-10.8
SE	6.94	5.35
95% CI	(-24.89, 2.32)	(-21.30, -0.32)
LS mean difference (tofersen - placebo)		0.5
SE		7.70
95% CI		(-14.62, 15.57)
p-value		0.9507
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.42, 1.02)
p-value		0.4207

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-eq5vas-anc-mi-sgrp.sas:t-cf-eq5vas-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.9187	0.8781	0.8679
Baseline disease duration since symptom onset by median	0.1464	0.1450	0.2068
Baseline NfL plasma level by median	0.9184	0.8859	0.3721
Riluzole or edaravone use	0.2065	0.1837	0.1651
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.5819	0.6561	0.8443
Age at first dose (<55, >=55)	0.5733	0.5506	0.8421

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 19JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	29.0	19.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.69
SE of log(RR)		0.562
95% CI		(0.228, 2.070)
p-value		0.5056
Adjusted OR - Odds Ratio (tofersen/placebo)		0.66
SE of log(OR)		0.676
95% CI		(0.174, 2.471)
p-value		0.5338
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.135
95% CI		(-0.364, 0.166)
p-value		0.4641

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	43.3	30.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.336
95% CI		(0.381, 1.419)
p-value		0.3594
Adjusted OR - Odds Ratio (tofersen/placebo)		0.57
SE of log(OR)		0.640
95% CI		(0.163, 1.995)
p-value		0.3785
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.136
95% CI		(-0.398, 0.136)
p-value		0.3375

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	34.8	35.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.16
SE of log(RR)		0.435
95% CI		(0.493, 2.719)
p-value		0.7363
Adjusted OR - Odds Ratio (tofersen/placebo)		1.24
SE of log(OR)		0.630
95% CI		(0.361, 4.274)
p-value		0.7308
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.149
95% CI		(-0.281, 0.304)
p-value		0.9402

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	37.8	14.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.39
SE of log(RR)		0.615
95% CI		(0.116, 1.295)
p-value		0.1236
Adjusted OR - Odds Ratio (tofersen/placebo)		0.32
SE of log(OR)		0.693
95% CI		(0.082, 1.234)
p-value		0.0976
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.23
SE of ARR		0.124
95% CI		(-0.478, 0.010)
p-value		0.0596

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	15.0	8.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.59
SE of log(RR)		1.025
95% CI		(0.079, 4.392)
p-value		0.6049
Adjusted OR - Odds Ratio (tofersen/placebo)		0.58
SE of log(OR)		1.023
95% CI		(0.077, 4.283)
p-value		0.5899
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.096
95% CI		(-0.253, 0.123)
p-value		0.4958

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

Page: 2 of 2

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	63.5	41.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.339
95% CI		(0.338, 1.276)
p-value		0.2149
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.602
95% CI		(0.149, 1.580)
p-value		0.2303
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.22
SE of ARR		0.148
95% CI		(-0.514, 0.068)
p-value		0.1329

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	27.0	27.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.421
95% CI		(0.451, 2.353)
p-value		0.9429
Adjusted OR - Odds Ratio (tofersen/placebo)		1.04
SE of log(OR)		0.600
95% CI		(0.322, 3.388)
p-value		0.9426
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.116
95% CI		(-0.228, 0.228)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	51.6	23.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.46
SE of log(RR)		0.471
95% CI		(0.184, 1.168)
p-value		0.1028
Adjusted OR - Odds Ratio (tofersen/placebo)		0.29
SE of log(OR)		0.760
95% CI		(0.065, 1.275)
p-value		0.1010
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.28
SE of ARR		0.164
95% CI		(-0.600, 0.042)
p-value		0.0884

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	43.9	35.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.357
95% CI		(0.401, 1.625)
p-value		0.5489
Adjusted OR - Odds Ratio (tofersen/placebo)		0.72
SE of log(OR)		0.548
95% CI		(0.248, 2.122)
p-value		0.5571
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.136
95% CI		(-0.351, 0.183)
p-value		0.5392

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	26.3	14.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.54
SE of log(RR)		0.630
95% CI		(0.158, 1.861)
p-value		0.3304
Adjusted OR - Odds Ratio (tofersen/placebo)		0.47
SE of log(OR)		0.785
95% CI		(0.102, 2.203)
p-value		0.3403
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.131
95% CI		(-0.378, 0.136)
p-value		0.3562

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	35.5	26.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.62
SE of log(RR)		0.405
95% CI		(0.280, 1.370)
p-value		0.2365
Adjusted OR - Odds Ratio (tofersen/placebo)		0.51
SE of log(OR)		0.581
95% CI		(0.164, 1.606)
p-value		0.2520
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.121
95% CI		(-0.331, 0.144)
p-value		0.4412

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in EQ-5D VAS score >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	38.5	25.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.94
SE of log(RR)		0.619
95% CI		(0.279, 3.158)
p-value		0.9175
Adjusted OR - Odds Ratio (tofersen/placebo)		0.94
SE of log(OR)		0.830
95% CI		(0.185, 4.773)
p-value		0.9392
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.163
95% CI		(-0.453, 0.185)
p-value		0.4104

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-wor-wk28-sgrp.sas:t-cf-eq5d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of improvement in EQ-5D VAS by >= 15% at week 28 using MI: treatment by subgroup interaction – ITT population

Subgroup analyses not performed. Condition of having at least 10 events in at least one of the subgroup categories for binary endpoint is not met.

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.9896
Baseline disease duration since symptom onset by median	0.3844
Baseline NfL plasma level by median	0.1544
Riluzole or edaravone use	0.0982
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1040
Age at first dose (<55, >=55)	0.8964

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline FSS total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	23 (79.3)
Number of imputed values per imputation	2 (11.8)	6 (20.7)
LS mean change from baseline	4.0	2.4
SE	2.88	2.31
95% CI	(-1.68, 9.61)	(-2.14, 6.90)
LS mean difference (tofersen - placebo)		-1.6
SE		3.46
95% CI		(-8.37, 5.20)
p-value		0.6470
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.70, 0.60)
p-value		0.8908

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	16 (84.2)	38 (88.4)
Number of imputed values per imputation	3 (15.8)	5 (11.6)
LS mean change from baseline	5.0	3.2
SE	3.94	3.14
95% CI	(-2.75, 12.69)	(-2.93, 9.40)
LS mean difference (tofersen - placebo)		-1.7
SE		3.78
95% CI		(-9.15, 5.68)
p-value		0.6467
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.81, 0.36)
p-value		0.4548

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	10.1	5.4
SE	3.71	2.82
95% CI	(2.85, 17.40)	(-0.11, 10.97)
LS mean difference (tofersen - placebo)		-4.7
SE		3.68
95% CI		(-11.91, 2.52)
p-value		0.2022
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.94, 0.35)
p-value		0.3700

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (85.7)	27 (79.4)
Number of imputed values per imputation	3 (14.3)	7 (20.6)
LS mean change from baseline	2.9	2.8
SE	3.21	2.64
95% CI	(-3.43, 9.16)	(-2.36, 7.97)
LS mean difference (tofersen - placebo)		-0.1
SE		3.74
95% CI		(-7.40, 7.28)
p-value		0.9875
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.63, 0.56)
p-value		0.9074

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	1.2	2.2
SE	2.36	1.98
95% CI	(-3.40, 5.84)	(-1.71, 6.05)
LS mean difference (tofersen - placebo)		0.9
SE		2.82
95% CI		(-4.57, 6.47)
p-value		0.7360
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.60, 0.58)
p-value		0.9685

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (81.3)	32 (84.2)
Number of imputed values per imputation	3 (18.8)	6 (15.8)
LS mean change from baseline	13.9	6.4
SE	4.04	3.06
95% CI	(6.02, 21.87)	(0.43, 12.45)
LS mean difference (tofersen - placebo)		-7.5
SE		4.04
95% CI		(-15.42, 0.41)
p-value		0.0631
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.95, 0.35)
p-value		0.3647

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

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Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	42 (93.3)
Number of imputed values per imputation	3 (13.6)	3 (6.7)
LS mean change from baseline	3.7	4.9
SE	2.61	1.81
95% CI	(-1.40, 8.81)	(1.38, 8.50)
LS mean difference (tofersen - placebo)		1.2
SE		3.18
95% CI		(-5.00, 7.47)
p-value		0.6975
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.47, 0.62)
p-value		0.7813

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline FSS total score. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	19 (70.4)
Number of imputed values per imputation	2 (14.3)	8 (29.6)
LS mean change from baseline	9.0	1.9
SE	3.38	2.52
95% CI	(2.39, 15.65)	(-3.07, 6.79)
LS mean difference (tofersen - placebo)		-7.2
SE		4.19
95% CI		(-15.39, 1.06)
p-value		0.0877
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-1.16, 0.30)
p-value		0.2453

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline FSS total score. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	11.1	6.2
SE	3.27	2.77
95% CI	(4.72, 17.55)	(0.78, 11.62)
LS mean difference (tofersen - placebo)		-4.9
SE		3.24
95% CI		(-11.29, 1.42)
p-value		0.1283
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.92, 0.21)
p-value		0.2225

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	-0.5	2.3
SE	3.37	2.45
95% CI	(-7.12, 6.08)	(-2.47, 7.12)
LS mean difference (tofersen - placebo)		2.8
SE		3.86
95% CI		(-4.72, 10.40)
p-value		0.4613
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.46, 0.89)
p-value		0.5315

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	4.9	3.5
SE	3.06	2.31
95% CI	(-1.06, 10.94)	(-1.07, 7.97)
LS mean difference (tofersen - placebo)		-1.5
SE		3.26
95% CI		(-7.88, 4.90)
p-value		0.6476
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.63, 0.46)
p-value		0.7702

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: FSS total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	20 (76.9)
Number of imputed values per imputation	1 (7.7)	6 (23.1)
LS mean change from baseline	7.6	5.7
SE	3.76	3.01
95% CI	(0.22, 14.95)	(-0.22, 11.58)
LS mean difference (tofersen - placebo)		-1.9
SE		4.15
95% CI		(-10.04, 6.24)
p-value		0.6466
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.93, 0.51)
p-value		0.5704

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline FSS total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-fss-sgrp.sas:t-cf-exp-fss-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.5712	0.5986	0.9362
Baseline disease duration since symptom onset by median	0.4090	0.3613	0.4082
Baseline NfL plasma level by median	0.8016	0.6620	0.4850
Riluzole or edaravone use	0.7645	0.8226	0.8772
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1776	0.1238	0.0790
Age at first dose (<55, >=55)	0.6280	0.5807	0.2970

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 15JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in FSS total score > = 15%	37.4	30.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.69
SE of log(RR)		0.456
95% CI		(0.282, 1.684)
p-value		0.4139
Adjusted OR - Odds Ratio (tofersen/placebo)		0.56
SE of log(OR)		0.718
95% CI		(0.136, 2.274)
p-value		0.4143
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.151
95% CI		(-0.367, 0.226)
p-value		0.6431

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in FSS total score > = 15%	43.0	37.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.95
SE of log(RR)		0.338
95% CI		(0.491, 1.844)
p-value		0.8820
Adjusted OR - Odds Ratio (tofersen/placebo)		0.91
SE of log(OR)		0.599
95% CI		(0.282, 2.949)
p-value		0.8778
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.05
SE of ARR		0.143
95% CI		(-0.334, 0.227)
p-value		0.7096

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in FSS total score > = 15%	52.0	36.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.71
SE of log(RR)		0.343
95% CI		(0.364, 1.394)
p-value		0.3218
Adjusted OR - Odds Ratio (tofersen/placebo)		0.53
SE of log(OR)		0.673
95% CI		(0.141, 1.976)
p-value		0.3432
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.157
95% CI		(-0.467, 0.149)
p-value		0.3112

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in FSS total score > = 15%	32.0	33.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.16
SE of log(RR)		0.488
95% CI		(0.447, 3.030)
p-value		0.7561
Adjusted OR - Odds Ratio (tofersen/placebo)		1.22
SE of log(OR)		0.626
95% CI		(0.358, 4.168)
p-value		0.7503
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.136
95% CI		(-0.254, 0.278)
p-value		0.9286

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in FSS total score > = 15%	26.9	26.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.94
SE of log(RR)		0.623
95% CI		(0.277, 3.183)
p-value		0.9188
Adjusted OR - Odds Ratio (tofersen/placebo)		0.93
SE of log(OR)		0.666
95% CI		(0.251, 3.422)
p-value		0.9089
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.01
SE of ARR		0.128
95% CI		(-0.259, 0.245)
p-value		0.9569

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in FSS total score > = 15%	57.2	42.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.79
SE of log(RR)		0.294
95% CI		(0.444, 1.404)
p-value		0.4208
Adjusted OR - Odds Ratio (tofersen/placebo)		0.62
SE of log(OR)		0.644
95% CI		(0.175, 2.186)
p-value		0.4557
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.15
SE of ARR		0.156
95% CI		(-0.454, 0.158)
p-value		0.3439

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in FSS total score > = 15%	37.4	30.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.82
SE of log(RR)		0.388
95% CI		(0.385, 1.760)
p-value		0.6159
Adjusted OR - Odds Ratio (tofersen/placebo)		0.75
SE of log(OR)		0.566
95% CI		(0.247, 2.279)
p-value		0.6132
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.130
95% CI		(-0.323, 0.188)
p-value		0.6046

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: FSS = Fatigue Severity Scale.

Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in FSS total score > = 15%	45.1	41.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.97
SE of log(RR)		0.364
95% CI		(0.473, 1.971)
p-value		0.9232
Adjusted OR - Odds Ratio (tofersen/placebo)		0.93
SE of log(OR)		0.754
95% CI		(0.212, 4.069)
p-value		0.9212
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.169
95% CI		(-0.366, 0.297)
p-value		0.8387

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: FSS = Fatigue Severity Scale.

Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in FSS total score > = 15%	56.2	36.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.296
95% CI		(0.368, 1.173)
p-value		0.1554
Adjusted OR - Odds Ratio (tofersen/placebo)		0.45
SE of log(OR)		0.587
95% CI		(0.142, 1.417)
p-value		0.1717
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.20
SE of ARR		0.138
95% CI		(-0.469, 0.074)
p-value		0.1537

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in FSS total score > = 15%	18.2	32.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.84
SE of log(RR)		0.702
95% CI		(0.465, 7.292)
p-value		0.3851
Adjusted OR - Odds Ratio (tofersen/placebo)		2.04
SE of log(OR)		0.785
95% CI		(0.437, 9.492)
p-value		0.3646
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.137
95% CI		(-0.123, 0.414)
p-value		0.2884

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in FSS total score > = 15%	30.6	33.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.91
SE of log(RR)		0.413
95% CI		(0.404, 2.040)
p-value		0.8154
Adjusted OR - Odds Ratio (tofersen/placebo)		0.87
SE of log(OR)		0.588
95% CI		(0.274, 2.737)
p-value		0.8054
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.123
95% CI		(-0.217, 0.267)
p-value		0.8423

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in FSS total score >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in FSS total score > = 15%	57.6	37.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.531
95% CI		(0.231, 1.857)
p-value		0.4265
Adjusted OR - Odds Ratio (tofersen/placebo)		0.50
SE of log(OR)		0.788
95% CI		(0.107, 2.355)
p-value		0.3827
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.20
SE of ARR		0.175
95% CI		(-0.542, 0.144)
p-value		0.2559

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-wor-wk28-sgrp.sas:t-cf-fss-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of improvement in FSS total score by >=15% at Week 28 using MI: treatment by subgroup interaction – ITT population

Subgroup analyses not performed. Condition of having at least 10 events in at least one of the subgroup categories for binary endpoint is not met.

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.7620
Baseline disease duration since symptom onset by median	0.7879
Baseline NfL plasma level by median	0.1671
Riluzole or edaravone use	0.1605
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.4166
Age at first dose (<55, >=55)	0.5468

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline ALSAQ-5 total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	23 (79.3)
Number of imputed values per imputation	2 (11.8)	6 (20.7)
LS mean change from baseline	10.7	9.0
SE	4.45	3.60
95% CI	(1.93, 19.39)	(1.98, 16.10)
LS mean difference (tofersen - placebo)		-1.6
SE		5.36
95% CI		(-12.13, 8.88)
p-value		0.7619
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.90, 0.40)
p-value		0.4565

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	16 (84.2)	38 (88.4)
Number of imputed values per imputation	3 (15.8)	5 (11.6)
LS mean change from baseline	9.5	3.9
SE	4.57	3.64
95% CI	(0.53, 18.44)	(-3.20, 11.08)
LS mean difference (tofersen - placebo)		-5.5
SE		4.36
95% CI		(-14.10, 3.01)
p-value		0.2038
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.97, 0.21)
p-value		0.2044

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	18.1	14.1
SE	5.34	4.06
95% CI	(7.59, 28.54)	(6.10, 22.02)
LS mean difference (tofersen - placebo)		-4.0
SE		5.41
95% CI		(-14.60, 6.60)
p-value		0.4596
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.88, 0.41)
p-value		0.4730

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (85.7)	27 (79.4)
Number of imputed values per imputation	3 (14.3)	7 (20.6)
LS mean change from baseline	7.4	1.4
SE	3.71	3.04
95% CI	(0.11, 14.67)	(-4.57, 7.36)
LS mean difference (tofersen - placebo)		-6.0
SE		4.42
95% CI		(-14.65, 2.66)
p-value		0.1749
Hedge's g standardized mean difference (tofersen - placebo)		-0.5
95% CI		(-1.08, 0.13)
p-value		0.1227

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	1.9	0.4
SE	2.86	2.44
95% CI	(-3.74, 7.48)	(-4.43, 5.15)
LS mean difference (tofersen - placebo)		-1.5
SE		3.47
95% CI		(-8.32, 5.29)
p-value		0.6629
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.83, 0.35)
p-value		0.4319

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (81.3)	32 (84.2)
Number of imputed values per imputation	3 (18.8)	6 (15.8)
LS mean change from baseline	24.7	14.3
SE	5.34	4.10
95% CI	(14.22, 35.17)	(6.28, 22.33)
LS mean difference (tofersen - placebo)		-10.4
SE		5.41
95% CI		(-20.99, 0.21)
p-value		0.0546
Hedge's g standardized mean difference (tofersen - placebo)		-0.6
95% CI		(-1.23, 0.08)
p-value		0.0866

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	42 (93.3)
Number of imputed values per imputation	3 (13.6)	3 (6.7)
LS mean change from baseline	7.6	7.0
SE	3.21	2.19
95% CI	(1.32, 13.90)	(2.70, 11.30)
LS mean difference (tofersen - placebo)		-0.6
SE		3.87
95% CI		(-8.19, 6.98)
p-value		0.8757
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.65, 0.43)
p-value		0.6904

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline ALSAQ-5 total score. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	19 (70.4)
Number of imputed values per imputation	2 (14.3)	8 (29.6)
LS mean change from baseline	15.2	4.4
SE	5.11	3.82
95% CI	(5.18, 25.19)	(-3.14, 11.85)
LS mean difference (tofersen - placebo)		-10.8
SE		6.33
95% CI		(-23.24, 1.57)
p-value		0.0869
Hedge's g standardized mean difference (tofersen - placebo)		-0.6
95% CI		(-1.32, 0.16)
p-value		0.1232

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline ALSAQ-5 total score. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	19.7	14.0
SE	5.07	4.22
95% CI	(9.78, 29.64)	(5.77, 22.29)
LS mean difference (tofersen - placebo)		-5.7
SE		5.02
95% CI		(-15.52, 4.17)
p-value		0.2585
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.96, 0.18)
p-value		0.1823

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	2.9	1.3
SE	3.48	2.52
95% CI	(-3.87, 9.77)	(-3.63, 6.26)
LS mean difference (tofersen - placebo)		-1.6
SE		4.04
95% CI		(-9.55, 6.29)
p-value		0.6864
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.83, 0.53)
p-value		0.6685

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	13.4	7.0
SE	3.84	2.89
95% CI	(5.91, 20.97)	(1.33, 12.65)
LS mean difference (tofersen - placebo)		-6.5
SE		4.10
95% CI		(-14.49, 1.58)
p-value		0.1154
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.92, 0.18)
p-value		0.1836

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: ALSAQ-5 total score change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	20 (76.9)
Number of imputed values per imputation	1 (7.7)	6 (23.1)
LS mean change from baseline	7.7	6.1
SE	5.98	4.65
95% CI	(-4.05, 19.41)	(-2.97, 15.26)
LS mean difference (tofersen - placebo)		-1.5
SE		6.60
95% CI		(-14.47, 11.39)
p-value		0.8153
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.95, 0.49)
p-value		0.5335

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-Ârelated status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline ALSAQ-5 total score, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-aq5-anc-mi-sgrp.sas:t-cf-exp-aq5-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.2446	0.2266	0.1881
Baseline disease duration since symptom onset by median	0.9741	0.9849	0.9633
Baseline NfL plasma level by median	0.9229	0.5950	0.2587
Riluzole or edaravone use	0.8864	0.9233	0.9590
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.6554	0.5329	0.3818
Age at first dose (<55, >=55)	0.3927	0.3413	0.7459

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-cs-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 19JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	31.3	34.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.06
SE of log(RR)		0.503
95% CI		(0.395, 2.839)
p-value		0.9102
Adjusted OR - Odds Ratio (tofersen/placebo)		1.08
SE of log(OR)		0.668
95% CI		(0.293, 4.011)
p-value		0.9039
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.148
95% CI		(-0.258, 0.322)
p-value		0.8276

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	47.1	22.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.47
SE of log(RR)		0.415
95% CI		(0.210, 1.071)
p-value		0.0726
Adjusted OR - Odds Ratio (tofersen/placebo)		0.34
SE of log(OR)		0.598
95% CI		(0.107, 1.114)
p-value		0.0752
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.24
SE of ARR		0.134
95% CI		(-0.508, 0.018)
p-value		0.0683

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	46.2	27.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.410
95% CI		(0.297, 1.481)
p-value		0.3169
Adjusted OR - Odds Ratio (tofersen/placebo)		0.54
SE of log(OR)		0.648
95% CI		(0.152, 1.925)
p-value		0.3425
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.19
SE of ARR		0.153
95% CI		(-0.487, 0.111)
p-value		0.2182

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	34.9	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.95
SE of log(RR)		0.437
95% CI		(0.402, 2.228)
p-value		0.8999
Adjusted OR - Odds Ratio (tofersen/placebo)		0.92
SE of log(OR)		0.685
95% CI		(0.240, 3.521)
p-value		0.9018
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.132
95% CI		(-0.335, 0.184)
p-value		0.5691

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	15.2	15.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.09
SE of log(RR)		0.801
95% CI		(0.226, 5.226)
p-value		0.9175
Adjusted OR - Odds Ratio (tofersen/placebo)		1.10
SE of log(OR)		0.852
95% CI		(0.207, 5.840)
p-value		0.9120
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.102
95% CI		(-0.199, 0.201)
p-value		0.9956

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	70.2	38.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.57
SE of log(RR)		0.294
95% CI		(0.321, 1.017)
p-value		0.0570
Adjusted OR - Odds Ratio (tofersen/placebo)		0.33
SE of log(OR)		0.671
95% CI		(0.089, 1.234)
p-value		0.0997
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.32
SE of ARR		0.147
95% CI		(-0.608, -0.031)
p-value		0.0300

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	38.4	25.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.67
SE of log(RR)		0.379
95% CI		(0.317, 1.400)
p-value		0.2832
Adjusted OR - Odds Ratio (tofersen/placebo)		0.54
SE of log(OR)		0.583
95% CI		(0.172, 1.692)
p-value		0.2897
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.125
95% CI		(-0.379, 0.112)
p-value		0.2860

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	41.6	31.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.78
SE of log(RR)		0.441
95% CI		(0.327, 1.845)
p-value		0.5672
Adjusted OR - Odds Ratio (tofersen/placebo)		0.66
SE of log(OR)		0.741
95% CI		(0.154, 2.813)
p-value		0.5720
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.165
95% CI		(-0.425, 0.221)
p-value		0.5344

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	56.7	32.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.57
SE of log(RR)		0.327
95% CI		(0.299, 1.078)
p-value		0.0837
Adjusted OR - Odds Ratio (tofersen/placebo)		0.39
SE of log(OR)		0.567
95% CI		(0.130, 1.197)
p-value		0.1004
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.25
SE of ARR		0.136
95% CI		(-0.511, 0.021)
p-value		0.0705

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	15.6	21.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.39
SE of log(RR)		0.718
95% CI		(0.341, 5.677)
p-value		0.6459
Adjusted OR - Odds Ratio (tofersen/placebo)		1.51
SE of log(OR)		0.889
95% CI		(0.264, 8.634)
p-value		0.6426
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.123
95% CI		(-0.180, 0.301)
p-value		0.6228

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	39.8	26.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		0.346
95% CI		(0.283, 1.098)
p-value		0.0910
Adjusted OR - Odds Ratio (tofersen/placebo)		0.39
SE of log(OR)		0.609
95% CI		(0.117, 1.273)
p-value		0.1177
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.125
95% CI		(-0.375, 0.116)
p-value		0.3005

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	39.3	28.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.91
SE of log(RR)		0.542
95% CI		(0.314, 2.619)
p-value		0.8556
Adjusted OR - Odds Ratio (tofersen/placebo)		0.87
SE of log(OR)		0.778
95% CI		(0.189, 3.997)
p-value		0.8576
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.165
95% CI		(-0.434, 0.215)
p-value		0.5074

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-wor-wk28-sgrp.sas:t-cf-aq5-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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ALSA1-Difficult to Stand Up

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.5737	0.5821	0.9084
Baseline disease duration since symptom onset by median	0.4678	0.5873	0.5375
Baseline NfL plasma level by median	0.7904	0.4492	0.3144
Riluzole or edaravone use	0.6361	0.4272	0.5170
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.7750	0.5269	0.4176
Age at first dose (<55, >=55)	0.9042	0.8426	0.5305

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSA1-Difficulty Using My Arms and Hands

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.6385	0.6777	0.8184
Baseline disease duration since symptom onset by median	0.2691	0.2574	0.2730
Baseline NfL plasma level by median	0.5357	0.4524	0.4970
Riluzole or edaravone use	0.1271	0.1187	0.1269
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.2651	0.2269	0.1892
Age at first dose (<55, >=55)	0.5790	0.5694	0.2144

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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ALSA1-Difficulty Eating Solid Food

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.9572	0.9372	0.9542
Baseline disease duration since symptom onset by median	0.5423	0.5742	0.4848
Baseline NfL plasma level by median	0.7355	0.7642	0.6035
Riluzole or edaravone use	0.8095	0.8061	0.8200
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3753	0.3748	0.3935
Age at first dose (<55, >=55)	0.1190	0.0969	0.3532

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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ALSA1-My Speech Not Easy to Understand

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.6651	0.6735	0.7484
Baseline disease duration since symptom onset by median	0.7871	0.8312	0.7295
Baseline NfL plasma level by median	0.7989	0.7385	0.9018
Riluzole or edaravone use	0.4855	0.4871	0.4884
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3465	0.3418	0.3446
Age at first dose (<55, >=55)	0.1617	0.1515	0.3755

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

ALSA1-Felt Hopeless About the Future

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.3844	0.3746	0.3796
Baseline disease duration since symptom onset by median	0.6416	0.6328	0.5551
Baseline NfL plasma level by median	0.9064	0.9401	0.9930
Riluzole or edaravone use	0.4137	0.4141	0.4248
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.7031	0.7057	0.7062
Age at first dose (<55, >=55)	0.9858	0.9736	0.7503

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficult to Stand Up/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	55.4	32.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		0.376
95% CI		(0.268, 1.171)
p-value		0.1236
Adjusted OR - Odds Ratio (tofersen/placebo)		0.35
SE of log(OR)		0.721
95% CI		(0.086, 1.447)
p-value		0.1477
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.23
SE of ARR		0.154
95% CI		(-0.528, 0.076)
p-value		0.1421

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficult to Stand Up/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	59.3	39.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.297
95% CI		(0.410, 1.314)
p-value		0.2978
Adjusted OR - Odds Ratio (tofersen/placebo)		0.58
SE of log(OR)		0.547
95% CI		(0.198, 1.688)
p-value		0.3163
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.20
SE of ARR		0.139
95% CI		(-0.474, 0.069)
p-value		0.1441

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficulty Using My Arms and Hands/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	33.6	30.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.77
SE of log(RR)		0.451
95% CI		(0.318, 1.867)
p-value		0.5638
Adjusted OR - Odds Ratio (tofersen/placebo)		0.65
SE of log(OR)		0.771
95% CI		(0.144, 2.961)
p-value		0.5815
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.151
95% CI		(-0.331, 0.262)
p-value		0.8184

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Difficulty Using My Arms and Hands/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	43.7	45.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.00
SE of log(RR)		0.310
95% CI		(0.545, 1.833)
p-value		0.9974
Adjusted OR - Odds Ratio (tofersen/placebo)		0.99
SE of log(OR)		0.627
95% CI		(0.290, 3.391)
p-value		0.9903
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.142
95% CI		(-0.265, 0.292)
p-value		0.9249

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Difficulty Eating Solid Food/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	35.3	37.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.05
SE of log(RR)		0.402
95% CI		(0.477, 2.301)
p-value		0.9088
Adjusted OR - Odds Ratio (tofersen/placebo)		1.08
SE of log(OR)		0.653
95% CI		(0.300, 3.890)
p-value		0.9053
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.148
95% CI		(-0.272, 0.310)
p-value		0.8974

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Difficulty Eating Solid Food/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	18.8	19.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.01
SE of log(RR)		0.643
95% CI		(0.285, 3.544)
p-value		0.9934
Adjusted OR - Odds Ratio (tofersen/placebo)		1.00
SE of log(OR)		0.722
95% CI		(0.243, 4.123)
p-value		0.9989
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.114
95% CI		(-0.214, 0.231)
p-value		0.9412

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-My Speech Not Easy to Understand/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	22.3	20.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.627
95% CI		(0.238, 2.781)
p-value		0.7418
Adjusted OR - Odds Ratio (tofersen/placebo)		0.78
SE of log(OR)		0.801
95% CI		(0.162, 3.740)
p-value		0.7539
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.130
95% CI		(-0.278, 0.232)
p-value		0.8599

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-My Speech Not Easy to Understand/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	19.4	22.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.18
SE of log(RR)		0.590
95% CI		(0.371, 3.754)
p-value		0.7785
Adjusted OR - Odds Ratio (tofersen/placebo)		1.22
SE of log(OR)		0.710
95% CI		(0.304, 4.910)
p-value		0.7784
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.115
95% CI		(-0.193, 0.259)
p-value		0.7761

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Felt Hopeless About the Future/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	21.7	30.1
Adjusted RR - Relative Risk (tofersen/placebo)		1.44
SE of log(RR)		0.601
95% CI		(0.444, 4.677)
p-value		0.5430
Adjusted OR - Odds Ratio (tofersen/placebo)		1.58
SE of log(OR)		0.739
95% CI		(0.372, 6.748)
p-value		0.5342
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.136
95% CI		(-0.183, 0.351)
p-value		0.5360

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Felt Hopeless About the Future/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	28.4	20.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.72
SE of log(RR)		0.540
95% CI		(0.249, 2.060)
p-value		0.5351
Adjusted OR - Odds Ratio (tofersen/placebo)		0.65
SE of log(OR)		0.683
95% CI		(0.170, 2.480)
p-value		0.5283
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.126
95% CI		(-0.326, 0.169)
p-value		0.5344

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficult to Stand Up/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	59.1	43.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.78
SE of log(RR)		0.295
95% CI		(0.436, 1.386)
p-value		0.3940
Adjusted OR - Odds Ratio (tofersen/placebo)		0.60
SE of log(OR)		0.631
95% CI		(0.175, 2.074)
p-value		0.4212
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.15
SE of ARR		0.153
95% CI		(-0.451, 0.147)
p-value		0.3194

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficult to Stand Up/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	56.3	28.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.55
SE of log(RR)		0.388
95% CI		(0.255, 1.167)
p-value		0.1182
Adjusted OR - Odds Ratio (tofersen/placebo)		0.37
SE of log(OR)		0.619
95% CI		(0.110, 1.252)
p-value		0.1103
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.28
SE of ARR		0.140
95% CI		(-0.553, -0.006)
p-value		0.0449

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	61.5	46.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.296
95% CI		(0.452, 1.442)
p-value		0.4700
Adjusted OR - Odds Ratio (tofersen/placebo)		0.65
SE of log(OR)		0.630
95% CI		(0.188, 2.227)
p-value		0.4902
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.15
SE of ARR		0.157
95% CI		(-0.456, 0.159)
p-value		0.3451

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	22.8	30.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.64
SE of log(RR)		0.558
95% CI		(0.548, 4.890)
p-value		0.3779
Adjusted OR - Odds Ratio (tofersen/placebo)		2.04
SE of log(OR)		0.775
95% CI		(0.446, 9.304)
p-value		0.3586
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.128
95% CI		(-0.174, 0.328)
p-value		0.5491

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Eating Solid Food/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	23.8	30.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.48
SE of log(RR)		0.566
95% CI		(0.487, 4.476)
p-value		0.4918
Adjusted OR - Odds Ratio (tofersen/placebo)		1.68
SE of log(OR)		0.728
95% CI		(0.403, 6.983)
p-value		0.4770
ARR - Absolute Risk Reduction (tofersen - placebo)		0.07
SE of ARR		0.141
95% CI		(-0.207, 0.344)
p-value		0.6272

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Eating Solid Food/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	28.6	22.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.96
SE of log(RR)		0.419
95% CI		(0.422, 2.182)
p-value		0.9227
Adjusted OR - Odds Ratio (tofersen/placebo)		0.94
SE of log(OR)		0.726
95% CI		(0.227, 3.904)
p-value		0.9327
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.123
95% CI		(-0.303, 0.178)
p-value		0.6109

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-My Speech Not Easy to Understand/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	17.7	22.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.43
SE of log(RR)		0.688
95% CI		(0.371, 5.512)
p-value		0.6026
Adjusted OR - Odds Ratio (tofersen/placebo)		1.53
SE of log(OR)		0.801
95% CI		(0.318, 7.370)
p-value		0.5946
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.124
95% CI		(-0.201, 0.286)
p-value		0.7316

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-My Speech Not Easy to Understand/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	22.9	21.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.14
SE of log(RR)		0.507
95% CI		(0.420, 3.069)
p-value		0.8021
Adjusted OR - Odds Ratio (tofersen/placebo)		1.21
SE of log(OR)		0.760
95% CI		(0.273, 5.368)
p-value		0.8019
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.121
95% CI		(-0.255, 0.220)
p-value		0.8852

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Felt Hopeless About the Future/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	21.8	26.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.26
SE of log(RR)		0.605
95% CI		(0.385, 4.137)
p-value		0.7000
Adjusted OR - Odds Ratio (tofersen/placebo)		1.34
SE of log(OR)		0.743
95% CI		(0.312, 5.743)
p-value		0.6942
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.135
95% CI		(-0.214, 0.314)
p-value		0.7126

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Felt Hopeless About the Future/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	27.7	21.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.86
SE of log(RR)		0.565
95% CI		(0.284, 2.603)
p-value		0.7886
Adjusted OR - Odds Ratio (tofersen/placebo)		0.83
SE of log(OR)		0.688
95% CI		(0.215, 3.183)
p-value		0.7818
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.126
95% CI		(-0.305, 0.187)
p-value		0.6390

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSA1-Difficult to Stand Up/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	43.4	30.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.477
95% CI		(0.261, 1.688)
p-value		0.3886
Adjusted OR - Odds Ratio (tofersen/placebo)		0.58
SE of log(OR)		0.598
95% CI		(0.180, 1.877)
p-value		0.3641
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.141
95% CI		(-0.406, 0.146)
p-value		0.3546

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficult to Stand Up/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	75.1	42.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.57
SE of log(RR)		0.272
95% CI		(0.336, 0.977)
p-value		0.0407
Adjusted OR - Odds Ratio (tofersen/placebo)		0.29
SE of log(OR)		0.702
95% CI		(0.073, 1.142)
p-value		0.0765
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.33
SE of ARR		0.140
95% CI		(-0.604, -0.057)
p-value		0.0180

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	21.5	25.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.22
SE of log(RR)		0.627
95% CI		(0.356, 4.151)
p-value		0.7557
Adjusted OR - Odds Ratio (tofersen/placebo)		1.28
SE of log(OR)		0.751
95% CI		(0.294, 5.591)
p-value		0.7407
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.122
95% CI		(-0.200, 0.278)
p-value		0.7480

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSA1-Difficulty Using My Arms and Hands/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	60.8	51.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.79
SE of log(RR)		0.288
95% CI		(0.450, 1.394)
p-value		0.4194
Adjusted OR - Odds Ratio (tofersen/placebo)		0.61
SE of log(OR)		0.649
95% CI		(0.170, 2.167)
p-value		0.4424
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.155
95% CI		(-0.399, 0.208)
p-value		0.5390

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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ALSA1-Difficulty Eating Solid Food/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	10.1	12.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.40
SE of log(RR)		0.799
95% CI		(0.292, 6.701)
p-value		0.6740
Adjusted OR - Odds Ratio (tofersen/placebo)		1.54
SE of log(OR)		1.001
95% CI		(0.216, 10.951)
p-value		0.6663
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.088
95% CI		(-0.153, 0.191)
p-value		0.8268

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficulty Eating Solid Food/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	47.3	39.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.04
SE of log(RR)		0.363
95% CI		(0.510, 2.120)
p-value		0.9140
Adjusted OR - Odds Ratio (tofersen/placebo)		1.07
SE of log(OR)		0.665
95% CI		(0.292, 3.950)
p-value		0.9155
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.155
95% CI		(-0.377, 0.230)
p-value		0.6347

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-My Speech Not Easy to Understand/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	10.3	8.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.95
SE of log(RR)		1.114
95% CI		(0.106, 8.402)
p-value		0.9599
Adjusted OR - Odds Ratio (tofersen/placebo)		0.96
SE of log(OR)		1.110
95% CI		(0.109, 8.468)
p-value		0.9713
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.086
95% CI		(-0.191, 0.146)
p-value		0.7937

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-My Speech Not Easy to Understand/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	33.9	33.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.29
SE of log(RR)		0.458
95% CI		(0.524, 3.159)
p-value		0.5830
Adjusted OR - Odds Ratio (tofersen/placebo)		1.50
SE of log(OR)		0.723
95% CI		(0.363, 6.176)
p-value		0.5762
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.148
95% CI		(-0.291, 0.288)
p-value		0.9925

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Felt Hopeless About the Future/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	15.9	13.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.784
95% CI		(0.175, 3.778)
p-value		0.7909
Adjusted OR - Odds Ratio (tofersen/placebo)		0.80
SE of log(OR)		0.855
95% CI		(0.149, 4.261)
p-value		0.7911
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.104
95% CI		(-0.229, 0.179)
p-value		0.8102

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Felt Hopeless About the Future/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	37.0	34.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.90
SE of log(RR)		0.435
95% CI		(0.385, 2.117)
p-value		0.8135
Adjusted OR - Odds Ratio (tofersen/placebo)		0.86
SE of log(OR)		0.645
95% CI		(0.244, 3.058)
p-value		0.8207
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.151
95% CI		(-0.323, 0.270)
p-value		0.8606

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Difficult to Stand Up/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	52.5	36.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.71
SE of log(RR)		0.293
95% CI		(0.398, 1.255)
p-value		0.2362
Adjusted OR - Odds Ratio (tofersen/placebo)		0.53
SE of log(OR)		0.548
95% CI		(0.182, 1.561)
p-value		0.2510
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.133
95% CI		(-0.417, 0.104)
p-value		0.2398

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Difficult to Stand Up/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	65.2	35.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.58
SE of log(RR)		0.301
95% CI		(0.321, 1.044)
p-value		0.0691
Adjusted OR - Odds Ratio (tofersen/placebo)		0.24
SE of log(OR)		0.838
95% CI		(0.046, 1.241)
p-value		0.0887
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.29
SE of ARR		0.163
95% CI		(-0.612, 0.026)
p-value		0.0717

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Difficulty Using My Arms and Hands/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	31.8	44.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.44
SE of log(RR)		0.355
95% CI		(0.721, 2.895)
p-value		0.2999
Adjusted OR - Odds Ratio (tofersen/placebo)		1.99
SE of log(OR)		0.631
95% CI		(0.577, 6.844)
p-value		0.2764
ARR - Absolute Risk Reduction (tofersen - placebo)		0.12
SE of ARR		0.129
95% CI		(-0.127, 0.377)
p-value		0.3311

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Difficulty Using My Arms and Hands/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	50.2	30.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.62
SE of log(RR)		0.425
95% CI		(0.268, 1.418)
p-value		0.2553
Adjusted OR - Odds Ratio (tofersen/placebo)		0.44
SE of log(OR)		0.732
95% CI		(0.104, 1.830)
p-value		0.2567
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.20
SE of ARR		0.168
95% CI		(-0.527, 0.130)
p-value		0.2355

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Difficulty Eating Solid Food/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	28.6	30.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.09
SE of log(RR)		0.402
95% CI		(0.498, 2.405)
p-value		0.8224
Adjusted OR - Odds Ratio (tofersen/placebo)		1.14
SE of log(OR)		0.596
95% CI		(0.355, 3.668)
p-value		0.8241
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.120
95% CI		(-0.219, 0.252)
p-value		0.8903

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Difficulty Eating Solid Food/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	23.5	20.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.91
SE of log(RR)		0.641
95% CI		(0.260, 3.203)
p-value		0.8856
Adjusted OR - Odds Ratio (tofersen/placebo)		0.89
SE of log(OR)		0.839
95% CI		(0.171, 4.593)
p-value		0.8860
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.144
95% CI		(-0.308, 0.256)
p-value		0.8561

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-My Speech Not Easy to Understand/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	18.0	23.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.35
SE of log(RR)		0.552
95% CI		(0.457, 3.983)
p-value		0.5877
Adjusted OR - Odds Ratio (tofersen/placebo)		1.45
SE of log(OR)		0.683
95% CI		(0.381, 5.542)
p-value		0.5838
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.107
95% CI		(-0.154, 0.266)
p-value		0.6030

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-My Speech Not Easy to Understand/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	25.0	18.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.653
95% CI		(0.207, 2.677)
p-value		0.6506
Adjusted OR - Odds Ratio (tofersen/placebo)		0.68
SE of log(OR)		0.858
95% CI		(0.126, 3.654)
p-value		0.6525
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.143
95% CI		(-0.349, 0.213)
p-value		0.6345

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Felt Hopeless About the Future/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	21.9	27.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.26
SE of log(RR)		0.492
95% CI		(0.479, 3.296)
p-value		0.6427
Adjusted OR - Odds Ratio (tofersen/placebo)		1.35
SE of log(OR)		0.645
95% CI		(0.382, 4.792)
p-value		0.6392
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.114
95% CI		(-0.172, 0.274)
p-value		0.6559

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Felt Hopeless About the Future/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	30.6	20.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.65
SE of log(RR)		0.639
95% CI		(0.186, 2.272)
p-value		0.4992
Adjusted OR - Odds Ratio (tofersen/placebo)		0.58
SE of log(OR)		0.814
95% CI		(0.117, 2.854)
p-value		0.5018
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.155
95% CI		(-0.408, 0.201)
p-value		0.5069

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficult to Stand Up/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	70.7	43.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.62
SE of log(RR)		0.241
95% CI		(0.386, 0.994)
p-value		0.0473
Adjusted OR - Odds Ratio (tofersen/placebo)		0.34
SE of log(OR)		0.593
95% CI		(0.107, 1.092)
p-value		0.0701
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.27
SE of ARR		0.129
95% CI		(-0.526, -0.018)
p-value		0.0356

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficult to Stand Up/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	38.8	28.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.72
SE of log(RR)		0.465
95% CI		(0.289, 1.791)
p-value		0.4797
Adjusted OR - Odds Ratio (tofersen/placebo)		0.61
SE of log(OR)		0.701
95% CI		(0.155, 2.416)
p-value		0.4828
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.158
95% CI		(-0.415, 0.203)
p-value		0.5004

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Using My Arms and Hands/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	58.2	48.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.84
SE of log(RR)		0.273
95% CI		(0.489, 1.429)
p-value		0.5130
Adjusted OR - Odds Ratio (tofersen/placebo)		0.71
SE of log(OR)		0.544
95% CI		(0.243, 2.048)
p-value		0.5214
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.139
95% CI		(-0.366, 0.180)
p-value		0.5039

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Using My Arms and Hands/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	12.0	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		2.44
SE of log(RR)		0.917
95% CI		(0.405, 14.761)
p-value		0.3299
Adjusted OR - Odds Ratio (tofersen/placebo)		2.98
SE of log(OR)		1.051
95% CI		(0.380, 23.449)
p-value		0.2983
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.124
95% CI		(-0.089, 0.397)
p-value		0.2136

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NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Eating Solid Food/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	31.3	38.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.23
SE of log(RR)		0.406
95% CI		(0.556, 2.737)
p-value		0.6050
Adjusted OR - Odds Ratio (tofersen/placebo)		1.37
SE of log(OR)		0.589
95% CI		(0.430, 4.332)
p-value		0.5969
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.133
95% CI		(-0.185, 0.337)
p-value		0.5693

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Eating Solid Food/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	20.0	12.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.61
SE of log(RR)		0.687
95% CI		(0.158, 2.332)
p-value		0.4671
Adjusted OR - Odds Ratio (tofersen/placebo)		0.54
SE of log(OR)		0.848
95% CI		(0.103, 2.870)
p-value		0.4736
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.118
95% CI		(-0.309, 0.155)
p-value		0.5171

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-My Speech Not Easy to Understand/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	22.1	30.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.38
SE of log(RR)		0.509
95% CI		(0.510, 3.753)
p-value		0.5244
Adjusted OR - Odds Ratio (tofersen/placebo)		1.52
SE of log(OR)		0.638
95% CI		(0.435, 5.299)
p-value		0.5121
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.121
95% CI		(-0.153, 0.321)
p-value		0.4868

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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ALSA1-My Speech Not Easy to Understand/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	18.8	11.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.57
SE of log(RR)		0.784
95% CI		(0.123, 2.662)
p-value		0.4766
Adjusted OR - Odds Ratio (tofersen/placebo)		0.51
SE of log(OR)		0.953
95% CI		(0.079, 3.301)
p-value		0.4790
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.121
95% CI		(-0.315, 0.159)
p-value		0.5194

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Felt Hopeless About the Future/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	29.9	26.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.87
SE of log(RR)		0.470
95% CI		(0.348, 2.194)
p-value		0.7736
Adjusted OR - Odds Ratio (tofersen/placebo)		0.84
SE of log(OR)		0.607
95% CI		(0.257, 2.771)
p-value		0.7790
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.127
95% CI		(-0.285, 0.214)
p-value		0.7819

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Felt Hopeless About the Future/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	18.8	22.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.20
SE of log(RR)		0.684
95% CI		(0.314, 4.586)
p-value		0.7908
Adjusted OR - Odds Ratio (tofersen/placebo)		1.25
SE of log(OR)		0.842
95% CI		(0.240, 6.501)
p-value		0.7921
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.132
95% CI		(-0.224, 0.292)
p-value		0.7971

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficult to Stand Up/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	59.5	43.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.248
95% CI		(0.405, 1.068)
p-value		0.0900
Adjusted OR - Odds Ratio (tofersen/placebo)		0.40
SE of log(OR)		0.597
95% CI		(0.124, 1.294)
p-value		0.1262
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.132
95% CI		(-0.420, 0.096)
p-value		0.2194

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficult to Stand Up/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	53.8	24.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.61
SE of log(RR)		0.547
95% CI		(0.209, 1.786)
p-value		0.3684
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.770
95% CI		(0.108, 2.201)
p-value		0.3497
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.29
SE of ARR		0.163
95% CI		(-0.613, 0.026)
p-value		0.0721

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Using My Arms and Hands/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	33.1	42.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.13
SE of log(RR)		0.327
95% CI		(0.598, 2.149)
p-value		0.7017
Adjusted OR - Odds Ratio (tofersen/placebo)		1.24
SE of log(OR)		0.581
95% CI		(0.398, 3.882)
p-value		0.7090
ARR - Absolute Risk Reduction (tofersen - placebo)		0.10
SE of ARR		0.127
95% CI		(-0.152, 0.347)
p-value		0.4430

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Using My Arms and Hands/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	49.3	32.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.505
95% CI		(0.301, 2.183)
p-value		0.6785
Adjusted OR - Odds Ratio (tofersen/placebo)		0.70
SE of log(OR)		0.824
95% CI		(0.139, 3.514)
p-value		0.6637
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.17
SE of ARR		0.173
95% CI		(-0.509, 0.169)
p-value		0.3255

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Eating Solid Food/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	27.3	20.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.63
SE of log(RR)		0.484
95% CI		(0.246, 1.640)
p-value		0.3477
Adjusted OR - Odds Ratio (tofersen/placebo)		0.55
SE of log(OR)		0.640
95% CI		(0.157, 1.934)
p-value		0.3525
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.113
95% CI		(-0.286, 0.158)
p-value		0.5707

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Eating Solid Food/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	25.3	37.0
Adjusted RR - Relative Risk (tofersen/placebo)		2.00
SE of log(RR)		0.550
95% CI		(0.679, 5.875)
p-value		0.2090
Adjusted OR - Odds Ratio (tofersen/placebo)		3.64
SE of log(OR)		0.938
95% CI		(0.579, 22.876)
p-value		0.1685
ARR - Absolute Risk Reduction (tofersen - placebo)		0.12
SE of ARR		0.159
95% CI		(-0.194, 0.428)
p-value		0.4609

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-My Speech Not Easy to Understand/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	23.0	18.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.65
SE of log(RR)		0.550
95% CI		(0.222, 1.918)
p-value		0.4376
Adjusted OR - Odds Ratio (tofersen/placebo)		0.59
SE of log(OR)		0.694
95% CI		(0.151, 2.285)
p-value		0.4420
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.05
SE of ARR		0.109
95% CI		(-0.264, 0.165)
p-value		0.6503

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-My Speech Not Easy to Understand/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	16.7	27.8
Adjusted RR - Relative Risk (tofersen/placebo)		2.50
SE of log(RR)		0.775
95% CI		(0.548, 11.435)
p-value		0.2364
Adjusted OR - Odds Ratio (tofersen/placebo)		3.46
SE of log(OR)		1.003
95% CI		(0.483, 24.699)
p-value		0.2166
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.142
95% CI		(-0.168, 0.390)
p-value		0.4366

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Felt Hopeless About the Future/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	22.0	23.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.99
SE of log(RR)		0.519
95% CI		(0.359, 2.751)
p-value		0.9908
Adjusted OR - Odds Ratio (tofersen/placebo)		0.99
SE of log(OR)		0.645
95% CI		(0.280, 3.515)
p-value		0.9901
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.112
95% CI		(-0.206, 0.235)
p-value		0.9000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-wor-wk28-sgrp.sas:t-cf-aq5-d-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Felt Hopeless About the Future/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	31.0	26.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.01
SE of log(RR)		0.687
95% CI		(0.262, 3.881)
p-value		0.9893
Adjusted OR - Odds Ratio (tofersen/placebo)		1.03
SE of log(OR)		0.846
95% CI		(0.196, 5.391)
p-value		0.9745
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.05
SE of ARR		0.159
95% CI		(-0.359, 0.264)
p-value		0.7640

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score by 15% at week 28 using MI: treatment by subgroup interaction

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ALSA1-Difficult to Stand Up

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.2725	0.3020	0.2405
Baseline disease duration since symptom onset by median	0.5292	0.5341	0.5399
Baseline NfL plasma level by median	0.7767	0.6962	0.5966
Riluzole or edaravone use	0.5079	0.4834	0.4312
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.9185	0.9236	0.8372
Age at first dose (<55, >=55)	0.6260	0.6201	0.7958

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,

Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score by 15% at week 28 using MI: treatment by subgroup interaction

ALSA1-Difficulty Using My Arms and Hands

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.9704	0.9571	0.8800
Baseline disease duration since symptom onset by median	0.5067	0.4527	0.3463
Baseline NfL plasma level by median	0.5543	0.5203	0.4690
Riluzole or edaravone use	0.8607	0.8416	0.7845
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.5900	0.5535	0.4462
Age at first dose (<55, >=55)	0.4492	0.5529	0.9700

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score by 15% at week 28 using MI: treatment by subgroup interaction

ALSA1-Difficulty Eating Solid Food

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	NA	NA	NA
Baseline disease duration since symptom onset by median	NA	NA	NA
Baseline NfL plasma level by median	NA	NA	NA
Riluzole or edaravone use	NA	NA	NA
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	NA	NA	NA

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score by 15% at week 28 using MI: treatment by subgroup interaction

ALSA1-My Speech Not Easy to Understand

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	NA	NA	NA
Baseline disease duration since symptom onset by median	NA	NA	NA
Baseline NfL plasma level by median	NA	NA	NA
Riluzole or edaravone use	NA	NA	NA
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	NA	NA	NA

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score by 15% at week 28 using MI: treatment by subgroup interaction

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ALSA1-Felt Hopeless About the Future

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.1648	0.1675	0.1265
Baseline disease duration since symptom onset by median	0.0732	0.0625	0.0415
Baseline NfL plasma level by median	0.1816	0.1627	0.0648
Riluzole or edaravone use	0.8502	0.8502	0.8514
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.4418	0.4361	0.4544
Age at first dose (<55, >=55)	0.8975	0.8930	0.8341

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories,
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficult to Stand Up/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	12.9	32.1
Adjusted RR - Relative Risk (tofersen/placebo)		2.30
SE of log(RR)		0.731
95% CI		(0.549, 9.652)
p-value		0.2540
Adjusted OR - Odds Ratio (tofersen/placebo)		2.39
SE of log(OR)		0.758
95% CI		(0.540, 10.554)
p-value		0.2514
ARR - Absolute Risk Reduction (tofersen - placebo)		0.19
SE of ARR		0.126
95% CI		(-0.054, 0.438)
p-value		0.1266

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficult to Stand Up/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	16.9	16.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.81
SE of log(RR)		0.611
95% CI		(0.245, 2.680)
p-value		0.7295
Adjusted OR - Odds Ratio (tofersen/placebo)		0.76
SE of log(OR)		0.806
95% CI		(0.157, 3.690)
p-value		0.7341
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.107
95% CI		(-0.211, 0.207)
p-value		0.9840

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
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233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

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ALSA1-Difficulty Using My Arms and Hands/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	17.6	26.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.83
SE of log(RR)		0.644
95% CI		(0.518, 6.473)
p-value		0.3476
Adjusted OR - Odds Ratio (tofersen/placebo)		2.36
SE of log(OR)		0.867
95% CI		(0.432, 12.924)
p-value		0.3214
ARR - Absolute Risk Reduction (tofersen - placebo)		0.09
SE of ARR		0.128
95% CI		(-0.164, 0.337)
p-value		0.4998

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Difficulty Using My Arms and Hands/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	13.0	24.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.90
SE of log(RR)		0.759
95% CI		(0.429, 8.416)
p-value		0.3976
Adjusted OR - Odds Ratio (tofersen/placebo)		2.21
SE of log(OR)		0.880
95% CI		(0.394, 12.390)
p-value		0.3673
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.107
95% CI		(-0.097, 0.321)
p-value		0.2954

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Felt Hopeless About the Future/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	5.9	19.4
Adjusted RR - Relative Risk (tofersen/placebo)		2.68
SE of log(RR)		0.893
95% CI		(0.465, 15.425)
p-value		0.2701
Adjusted OR - Odds Ratio (tofersen/placebo)		3.11
SE of log(OR)		1.058
95% CI		(0.391, 24.773)
p-value		0.2833
ARR - Absolute Risk Reduction (tofersen - placebo)		0.13
SE of ARR		0.096
95% CI		(-0.052, 0.322)
p-value		0.1578

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by gender - ITT population

ALSA1-Felt Hopeless About the Future/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	31.1	20.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.66
SE of log(RR)		0.470
95% CI		(0.262, 1.658)
p-value		0.3763
Adjusted OR - Odds Ratio (tofersen/placebo)		0.55
SE of log(OR)		0.683
95% CI		(0.144, 2.091)
p-value		0.3789
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.127
95% CI		(-0.356, 0.141)
p-value		0.3964

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficult to Stand Up/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	21.3	23.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.10
SE of log(RR)		0.636
95% CI		(0.316, 3.826)
p-value		0.8821
Adjusted OR - Odds Ratio (tofersen/placebo)		1.11
SE of log(OR)		0.740
95% CI		(0.261, 4.745)
p-value		0.8855
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.130
95% CI		(-0.236, 0.272)
p-value		0.8880

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficult to Stand Up/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	10.4	22.5
Adjusted RR - Relative Risk (tofersen/placebo)		2.04
SE of log(RR)		0.745
95% CI		(0.473, 8.765)
p-value		0.3393
Adjusted OR - Odds Ratio (tofersen/placebo)		2.22
SE of log(OR)		0.831
95% CI		(0.436, 11.334)
p-value		0.3361
ARR - Absolute Risk Reduction (tofersen - placebo)		0.12
SE of ARR		0.105
95% CI		(-0.085, 0.327)
p-value		0.2504

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	14.2	16.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.12
SE of log(RR)		0.769
95% CI		(0.248, 5.057)
p-value		0.8819
Adjusted OR - Odds Ratio (tofersen/placebo)		1.14
SE of log(OR)		0.903
95% CI		(0.195, 6.710)
p-value		0.8826
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.112
95% CI		(-0.192, 0.246)
p-value		0.8113

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.9	34.2
Adjusted RR - Relative Risk (tofersen/placebo)		2.13
SE of log(RR)		0.587
95% CI		(0.676, 6.744)
p-value		0.1963
Adjusted OR - Odds Ratio (tofersen/placebo)		2.79
SE of log(OR)		0.762
95% CI		(0.626, 12.395)
p-value		0.1786
ARR - Absolute Risk Reduction (tofersen - placebo)		0.18
SE of ARR		0.120
95% CI		(-0.054, 0.418)
p-value		0.1300

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Felt Hopeless About the Future/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	39.3	19.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		0.464
95% CI		(0.227, 1.396)
p-value		0.2146
Adjusted OR - Odds Ratio (tofersen/placebo)		0.43
SE of log(OR)		0.710
95% CI		(0.106, 1.710)
p-value		0.2286
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.19
SE of ARR		0.147
95% CI		(-0.482, 0.094)
p-value		0.1858

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

ALSA1-Felt Hopeless About the Future/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	4.8	20.0
Adjusted RR - Relative Risk (tofersen/placebo)		3.94
SE of log(RR)		0.984
95% CI		(0.573, 27.137)
p-value		0.1632
Adjusted OR - Odds Ratio (tofersen/placebo)		4.56
SE of log(OR)		1.058
95% CI		(0.574, 36.240)
p-value		0.1515
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.086
95% CI		(-0.016, 0.320)
p-value		0.0756

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficult to Stand Up/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.0	27.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.86
SE of log(RR)		0.601
95% CI		(0.573, 6.038)
p-value		0.3011
Adjusted OR - Odds Ratio (tofersen/placebo)		2.19
SE of log(OR)		0.750
95% CI		(0.504, 9.535)
p-value		0.2956
ARR - Absolute Risk Reduction (tofersen - placebo)		0.12
SE of ARR		0.114
95% CI		(-0.099, 0.348)
p-value		0.2756

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficult to Stand Up/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.0	18.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.40
SE of log(RR)		0.791
95% CI		(0.298, 6.614)
p-value		0.6680
Adjusted OR - Odds Ratio (tofersen/placebo)		1.42
SE of log(OR)		0.818
95% CI		(0.286, 7.055)
p-value		0.6680
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.117
95% CI		(-0.191, 0.267)
p-value		0.7447

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	16.8	33.1
Adjusted RR - Relative Risk (tofersen/placebo)		2.07
SE of log(RR)		0.600
95% CI		(0.637, 6.702)
p-value		0.2264
Adjusted OR - Odds Ratio (tofersen/placebo)		2.71
SE of log(OR)		0.801
95% CI		(0.565, 13.047)
p-value		0.2126
ARR - Absolute Risk Reduction (tofersen - placebo)		0.16
SE of ARR		0.122
95% CI		(-0.075, 0.402)
p-value		0.1791

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Difficulty Using My Arms and Hands/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	13.3	17.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.17
SE of log(RR)		0.742
95% CI		(0.274, 5.031)
p-value		0.8289
Adjusted OR - Odds Ratio (tofersen/placebo)		1.22
SE of log(OR)		0.941
95% CI		(0.194, 7.742)
p-value		0.8299
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.108
95% CI		(-0.168, 0.258)
p-value		0.6781

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Felt Hopeless About the Future/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	25.0	11.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.48
SE of log(RR)		0.682
95% CI		(0.126, 1.822)
p-value		0.2801
Adjusted OR - Odds Ratio (tofersen/placebo)		0.41
SE of log(OR)		0.807
95% CI		(0.084, 1.996)
p-value		0.2699
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.14
SE of ARR		0.113
95% CI		(-0.359, 0.083)
p-value		0.2207

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

ALSA1-Felt Hopeless About the Future/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	11.9	27.7
Adjusted RR - Relative Risk (tofersen/placebo)		2.06
SE of log(RR)		0.858
95% CI		(0.384, 11.100)
p-value		0.3986
Adjusted OR - Odds Ratio (tofersen/placebo)		2.33
SE of log(OR)		0.948
95% CI		(0.363, 14.938)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen - placebo)		0.16
SE of ARR		0.115
95% CI		(-0.066, 0.384)
p-value		0.1662

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Difficult to Stand Up/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.4	28.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.86
SE of log(RR)		0.584
95% CI		(0.593, 5.858)
p-value		0.2863
Adjusted OR - Odds Ratio (tofersen/placebo)		2.21
SE of log(OR)		0.717
95% CI		(0.542, 9.026)
p-value		0.2683
ARR - Absolute Risk Reduction (tofersen - placebo)		0.13
SE of ARR		0.106
95% CI		(-0.082, 0.334)
p-value		0.2360

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Difficult to Stand Up/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	14.3	14.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.93
SE of log(RR)		0.866
95% CI		(0.171, 5.105)
p-value		0.9377
Adjusted OR - Odds Ratio (tofersen/placebo)		0.93
SE of log(OR)		1.012
95% CI		(0.128, 6.756)
p-value		0.9420
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.120
95% CI		(-0.236, 0.236)
p-value		0.9982

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Difficulty Using My Arms and Hands/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.8	23.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.52
SE of log(RR)		0.591
95% CI		(0.477, 4.840)
p-value		0.4787
Adjusted OR - Odds Ratio (tofersen/placebo)		1.68
SE of log(OR)		0.713
95% CI		(0.414, 6.777)
p-value		0.4692
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.104
95% CI		(-0.123, 0.284)
p-value		0.4370

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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ALSA1-Difficulty Using My Arms and Hands/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	14.3	26.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.80
SE of log(RR)		0.747
95% CI		(0.415, 7.772)
p-value		0.4329
Adjusted OR - Odds Ratio (tofersen/placebo)		2.11
SE of log(OR)		0.910
95% CI		(0.355, 12.574)
p-value		0.4116
ARR - Absolute Risk Reduction (tofersen - placebo)		0.13
SE of ARR		0.132
95% CI		(-0.133, 0.386)
p-value		0.3383

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Felt Hopeless About the Future/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	21.4	20.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.01
SE of log(RR)		0.508
95% CI		(0.373, 2.725)
p-value		0.9880
Adjusted OR - Odds Ratio (tofersen/placebo)		1.01
SE of log(OR)		0.669
95% CI		(0.271, 3.739)
p-value		0.9912
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.109
95% CI		(-0.218, 0.209)
p-value		0.9636

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

ALSA1-Felt Hopeless About the Future/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.7	18.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.21
SE of log(RR)		0.801
95% CI		(0.251, 5.800)
p-value		0.8154
Adjusted OR - Odds Ratio (tofersen/placebo)		1.25
SE of log(OR)		0.944
95% CI		(0.197, 7.980)
p-value		0.8105
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.128
95% CI		(-0.224, 0.278)
p-value		0.8357

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficult to Stand Up/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.2	24.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.59
SE of log(RR)		0.627
95% CI		(0.467, 5.447)
p-value		0.4569
Adjusted OR - Odds Ratio (tofersen/placebo)		1.71
SE of log(OR)		0.711
95% CI		(0.423, 6.873)
p-value		0.4524
ARR - Absolute Risk Reduction (tofersen - placebo)		0.09
SE of ARR		0.108
95% CI		(-0.117, 0.306)
p-value		0.3823

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficult to Stand Up/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	14.6	20.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.44
SE of log(RR)		0.759
95% CI		(0.326, 6.380)
p-value		0.6296
Adjusted OR - Odds Ratio (tofersen/placebo)		1.53
SE of log(OR)		0.869
95% CI		(0.279, 8.412)
p-value		0.6231
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.121
95% CI		(-0.177, 0.299)
p-value		0.6154

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Using My Arms and Hands/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	14.9	18.9
Adjusted RR - Relative Risk (tofersen/placebo)		1.26
SE of log(RR)		0.635
95% CI		(0.363, 4.372)
p-value		0.7165
Adjusted OR - Odds Ratio (tofersen/placebo)		1.33
SE of log(OR)		0.768
95% CI		(0.294, 5.980)
p-value		0.7135
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.103
95% CI		(-0.162, 0.242)
p-value		0.6986

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Difficulty Using My Arms and Hands/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	15.6	32.3
Adjusted RR - Relative Risk (tofersen/placebo)		2.09
SE of log(RR)		0.688
95% CI		(0.542, 8.025)
p-value		0.2852
Adjusted OR - Odds Ratio (tofersen/placebo)		2.62
SE of log(OR)		0.855
95% CI		(0.491, 13.998)
p-value		0.2596
ARR - Absolute Risk Reduction (tofersen - placebo)		0.17
SE of ARR		0.130
95% CI		(-0.088, 0.421)
p-value		0.1997

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Felt Hopeless About the Future/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	28.1	24.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.87
SE of log(RR)		0.461
95% CI		(0.353, 2.148)
p-value		0.7635
Adjusted OR - Odds Ratio (tofersen/placebo)		0.82
SE of log(OR)		0.642
95% CI		(0.234, 2.898)
p-value		0.7623
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.123
95% CI		(-0.278, 0.206)
p-value		0.7700

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

ALSA1-Felt Hopeless About the Future/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	6.7	14.6
Adjusted RR - Relative Risk (tofersen/placebo)		2.12
SE of log(RR)		1.059
95% CI		(0.265, 16.877)
p-value		0.4794
Adjusted OR - Odds Ratio (tofersen/placebo)		2.32
SE of log(OR)		1.163
95% CI		(0.237, 22.630)
p-value		0.4702
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.092
95% CI		(-0.101, 0.258)
p-value		0.3896

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficult to Stand Up/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	9.5	19.1
Adjusted RR - Relative Risk (tofersen/placebo)		2.26
SE of log(RR)		0.733
95% CI		(0.538, 9.513)
p-value		0.2654
Adjusted OR - Odds Ratio (tofersen/placebo)		2.61
SE of log(OR)		0.831
95% CI		(0.512, 13.315)
p-value		0.2480
ARR - Absolute Risk Reduction (tofersen - placebo)		0.10
SE of ARR		0.088
95% CI		(-0.077, 0.268)
p-value		0.2791

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficult to Stand Up/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	24.6	29.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.40
SE of log(RR)		0.649
95% CI		(0.394, 5.012)
p-value		0.6004
Adjusted OR - Odds Ratio (tofersen/placebo)		1.48
SE of log(OR)		0.781
95% CI		(0.321, 6.863)
p-value		0.6129
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.155
95% CI		(-0.255, 0.354)
p-value		0.7513

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Using My Arms and Hands/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	10.2	20.3
Adjusted RR - Relative Risk (tofersen/placebo)		2.18
SE of log(RR)		0.705
95% CI		(0.548, 8.681)
p-value		0.2685
Adjusted OR - Odds Ratio (tofersen/placebo)		2.39
SE of log(OR)		0.781
95% CI		(0.516, 11.035)
p-value		0.2658
ARR - Absolute Risk Reduction (tofersen - placebo)		0.10
SE of ARR		0.090
95% CI		(-0.077, 0.278)
p-value		0.2655

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Difficulty Using My Arms and Hands/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	24.1	33.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.12
SE of log(RR)		0.527
95% CI		(0.398, 3.141)
p-value		0.8315
Adjusted OR - Odds Ratio (tofersen/placebo)		1.19
SE of log(OR)		0.875
95% CI		(0.214, 6.598)
p-value		0.8440
ARR - Absolute Risk Reduction (tofersen - placebo)		0.09
SE of ARR		0.156
95% CI		(-0.212, 0.399)
p-value		0.5473

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Felt Hopeless About the Future/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	18.3	20.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.05
SE of log(RR)		0.534
95% CI		(0.369, 2.991)
p-value		0.9259
Adjusted OR - Odds Ratio (tofersen/placebo)		1.06
SE of log(OR)		0.679
95% CI		(0.281, 4.024)
p-value		0.9285
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.103
95% CI		(-0.181, 0.223)
p-value		0.8397

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 28 using MI by age at first dose - ITT population

ALSA1-Felt Hopeless About the Future/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	20.8	19.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.18
SE of log(RR)		0.758
95% CI		(0.268, 5.237)
p-value		0.8234
Adjusted OR - Odds Ratio (tofersen/placebo)		1.26
SE of log(OR)		1.048
95% CI		(0.161, 9.803)
p-value		0.8269
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.141
95% CI		(-0.292, 0.260)
p-value		0.9108

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-sgrp.sas:t-cf-aq5-d-propim-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 10JUL2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

Physical Component Summary

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.1193
Baseline disease duration since symptom onset by median	0.6143
Baseline NfL plasma level by median	0.6572
Riluzole or edaravone use	0.5206
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.6319
Age at first dose (<55, >=55)	0.5441

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline SF-36 component summary, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

Mental Component Summary

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.9084
Baseline disease duration since symptom onset by median	0.8752
Baseline NfL plasma level by median	0.0268
Riluzole or edaravone use	0.4717
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1947
Age at first dose (<55, >=55)	0.7783

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline SF-36 component summary, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Mental Component Summary/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	23 (79.3)
Number of imputed values per imputation	2 (11.8)	6 (20.7)
LS mean change from baseline	-2.9	-0.7
SE	2.81	2.32
95% CI	(-8.45, 2.55)	(-5.25, 3.85)
LS mean difference (tofersen - placebo)		2.3
SE		3.41
95% CI		(-4.44, 8.94)
p-value		0.5095
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.49, 0.81)
p-value		0.6363

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Mental Component Summary/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	16 (84.2)	38 (88.4)
Number of imputed values per imputation	3 (15.8)	5 (11.6)
LS mean change from baseline	-1.9	-0.1
SE	2.87	2.25
95% CI	(-7.53, 3.74)	(-4.55, 4.27)
LS mean difference (tofersen - placebo)		1.8
SE		2.83
95% CI		(-3.79, 7.29)
p-value		0.5349
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.79)
p-value		0.4981

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

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Physical Component Summary/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	23 (79.3)
Number of imputed values per imputation	2 (11.8)	6 (20.7)
LS mean change from baseline	-2.9	-4.5
SE	1.91	1.54
95% CI	(-6.68, 0.79)	(-7.48, -1.45)
LS mean difference (tofersen - placebo)		-1.5
SE		2.30
95% CI		(-6.03, 2.99)
p-value		0.5085
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.69, 0.61)
p-value		0.8946

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Physical Component Summary/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	16 (84.2)	38 (88.4)
Number of imputed values per imputation	3 (15.8)	5 (11.6)
LS mean change from baseline	-4.9	-1.6
SE	2.08	1.65
95% CI	(-8.97, -0.81)	(-4.86, 1.61)
LS mean difference (tofersen - placebo)		3.3
SE		1.98
95% CI		(-0.62, 7.15)
p-value		0.0994
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.14, 1.04)
p-value		0.1352

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

Mental Component Summary/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-1.1	0.2
SE	3.05	2.31
95% CI	(-7.08, 4.89)	(-4.32, 4.74)
LS mean difference (tofersen - placebo)		1.3
SE		3.24
95% CI		(-5.05, 7.66)
p-value		0.6866
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.58, 0.70)
p-value		0.8608

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

Mental Component Summary/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (85.7)	27 (79.4)
Number of imputed values per imputation	3 (14.3)	7 (20.6)
LS mean change from baseline	-3.7	-1.6
SE	2.52	2.08
95% CI	(-8.60, 1.30)	(-5.70, 2.44)
LS mean difference (tofersen - placebo)		2.0
SE		2.96
95% CI		(-3.78, 7.82)
p-value		0.4948
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.82)
p-value		0.4753

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

Physical Component Summary/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	34 (89.5)
Number of imputed values per imputation	2 (13.3)	4 (10.5)
LS mean change from baseline	-8.6	-6.1
SE	2.27	1.72
95% CI	(-13.06, -4.18)	(-9.42, -2.69)
LS mean difference (tofersen - placebo)		2.6
SE		2.31
95% CI		(-1.95, 7.09)
p-value		0.2659
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.40, 0.88)
p-value		0.4672

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

Physical Component Summary/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (85.7)	27 (79.4)
Number of imputed values per imputation	3 (14.3)	7 (20.6)
LS mean change from baseline	-2.2	-1.0
SE	1.76	1.38
95% CI	(-5.68, 1.23)	(-3.72, 1.70)
LS mean difference (tofersen - placebo)		1.2
SE		2.08
95% CI		(-2.87, 5.29)
p-value		0.5599
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.27, 0.93)
p-value		0.2852

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

Mental Component Summary/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	0.4	-1.1
SE	2.00	1.72
95% CI	(-3.51, 4.34)	(-4.50, 2.23)
LS mean difference (tofersen - placebo)		-1.6
SE		2.43
95% CI		(-6.31, 3.21)
p-value		0.5235
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.76, 0.42)
p-value		0.5649

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

Mental Component Summary/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (81.3)	32 (84.2)
Number of imputed values per imputation	3 (18.8)	6 (15.8)
LS mean change from baseline	-6.8	1.1
SE	3.34	2.61
95% CI	(-13.31, -0.22)	(-4.00, 6.23)
LS mean difference (tofersen - placebo)		7.9
SE		3.52
95% CI		(0.98, 14.77)
p-value		0.0253
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.15, 1.16)
p-value		0.1286

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

Physical Component Summary/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	-3.1	-1.6
SE	1.52	1.26
95% CI	(-6.12, -0.15)	(-4.03, 0.89)
LS mean difference (tofersen - placebo)		1.6
SE		1.83
95% CI		(-2.02, 5.15)
p-value		0.3930
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.21, 0.98)
p-value		0.2000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

Physical Component Summary/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (81.3)	32 (84.2)
Number of imputed values per imputation	3 (18.8)	6 (15.8)
LS mean change from baseline	-7.6	-5.2
SE	2.45	1.86
95% CI	(-12.41, -2.79)	(-8.82, -1.52)
LS mean difference (tofersen - placebo)		2.4
SE		2.49
95% CI		(-2.46, 7.31)
p-value		0.3299
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.51, 0.78)
p-value		0.6898

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Mental Component Summary/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	42 (93.3)
Number of imputed values per imputation	3 (13.6)	3 (6.7)
LS mean change from baseline	-1.6	-0.8
SE	2.12	1.45
95% CI	(-5.73, 2.57)	(-3.67, 2.03)
LS mean difference (tofersen - placebo)		0.8
SE		2.56
95% CI		(-4.25, 5.77)
p-value		0.7661
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.42, 0.67)
p-value		0.6467

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline SF-36 component summary. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

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Mental Component Summary/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	19 (70.4)
Number of imputed values per imputation	2 (14.3)	8 (29.6)
LS mean change from baseline	-4.2	-0.5
SE	2.89	2.24
95% CI	(-9.85, 1.46)	(-4.86, 3.94)
LS mean difference (tofersen - placebo)		3.7
SE		3.70
95% CI		(-3.52, 10.99)
p-value		0.3132
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.47, 0.98)
p-value		0.4911

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline SF-36 component summary. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Physical Component Summary/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	42 (93.3)
Number of imputed values per imputation	3 (13.6)	3 (6.7)
LS mean change from baseline	-3.4	-3.1
SE	1.53	1.04
95% CI	(-6.37, -0.38)	(-5.17, -1.10)
LS mean difference (tofersen - placebo)		0.2
SE		1.85
95% CI		(-3.39, 3.87)
p-value		0.8975
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.39, 0.70)
p-value		0.5790

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline SF-36 component summary. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Physical Component Summary/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	12 (85.7)	19 (70.4)
Number of imputed values per imputation	2 (14.3)	8 (29.6)
LS mean change from baseline	-6.5	-4.1
SE	2.07	1.56
95% CI	(-10.56, -2.44)	(-7.15, -1.01)
LS mean difference (tofersen - placebo)		2.4
SE		2.59
95% CI		(-2.66, 7.50)
p-value		0.3503
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.45, 1.01)
p-value		0.4497

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, and baseline SF-36 component summary. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Mental Component Summary/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-3.4	0.3
SE	2.96	2.50
95% CI	(-9.23, 2.36)	(-4.56, 5.25)
LS mean difference (tofersen - placebo)		3.8
SE		3.06
95% CI		(-2.21, 9.77)
p-value		0.2164
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.19, 0.95)
p-value		0.1935

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Mental Component Summary/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	-0.6	-1.8
SE	2.46	1.78
95% CI	(-5.40, 4.25)	(-5.31, 1.67)
LS mean difference (tofersen - placebo)		-1.2
SE		2.83
95% CI		(-6.80, 4.31)
p-value		0.6607
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.82, 0.54)
p-value		0.6867

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Physical Component Summary/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	19 (90.5)	33 (84.6)
Number of imputed values per imputation	2 (9.5)	6 (15.4)
LS mean change from baseline	-7.9	-6.1
SE	2.08	1.75
95% CI	(-11.94, -3.80)	(-9.52, -2.66)
LS mean difference (tofersen - placebo)		1.8
SE		2.10
95% CI		(-2.34, 5.90)
p-value		0.3965
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.39, 0.74)
p-value		0.5540

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Physical Component Summary/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	-1.6	-1.0
SE	1.62	1.12
95% CI	(-4.81, 1.55)	(-3.20, 1.19)
LS mean difference (tofersen - placebo)		0.6
SE		1.86
95% CI		(-3.03, 4.27)
p-value		0.7392
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.44, 0.92)
p-value		0.4885

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

Mental Component Summary/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	-2.9	-0.5
SE	2.43	1.80
95% CI	(-7.62, 1.90)	(-4.03, 3.02)
LS mean difference (tofersen - placebo)		2.4
SE		2.58
95% CI		(-2.70, 7.42)
p-value		0.3610
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.29, 0.80)
p-value		0.3564

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

Mental Component Summary/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	20 (76.9)
Number of imputed values per imputation	1 (7.7)	6 (23.1)
LS mean change from baseline	-2.2	-1.0
SE	3.58	2.88
95% CI	(-9.18, 4.87)	(-6.62, 4.67)
LS mean difference (tofersen - placebo)		1.2
SE		4.11
95% CI		(-6.88, 9.24)
p-value		0.7739
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.66, 0.77)
p-value		0.8774

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

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Physical Component Summary/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	-3.9	-3.7
SE	1.84	1.37
95% CI	(-7.55, -0.32)	(-6.40, -1.02)
LS mean difference (tofersen - placebo)		0.2
SE		1.97
95% CI		(-3.64, 4.09)
p-value		0.9088
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.52, 0.57)
p-value		0.9253

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: SF-36 component summary change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

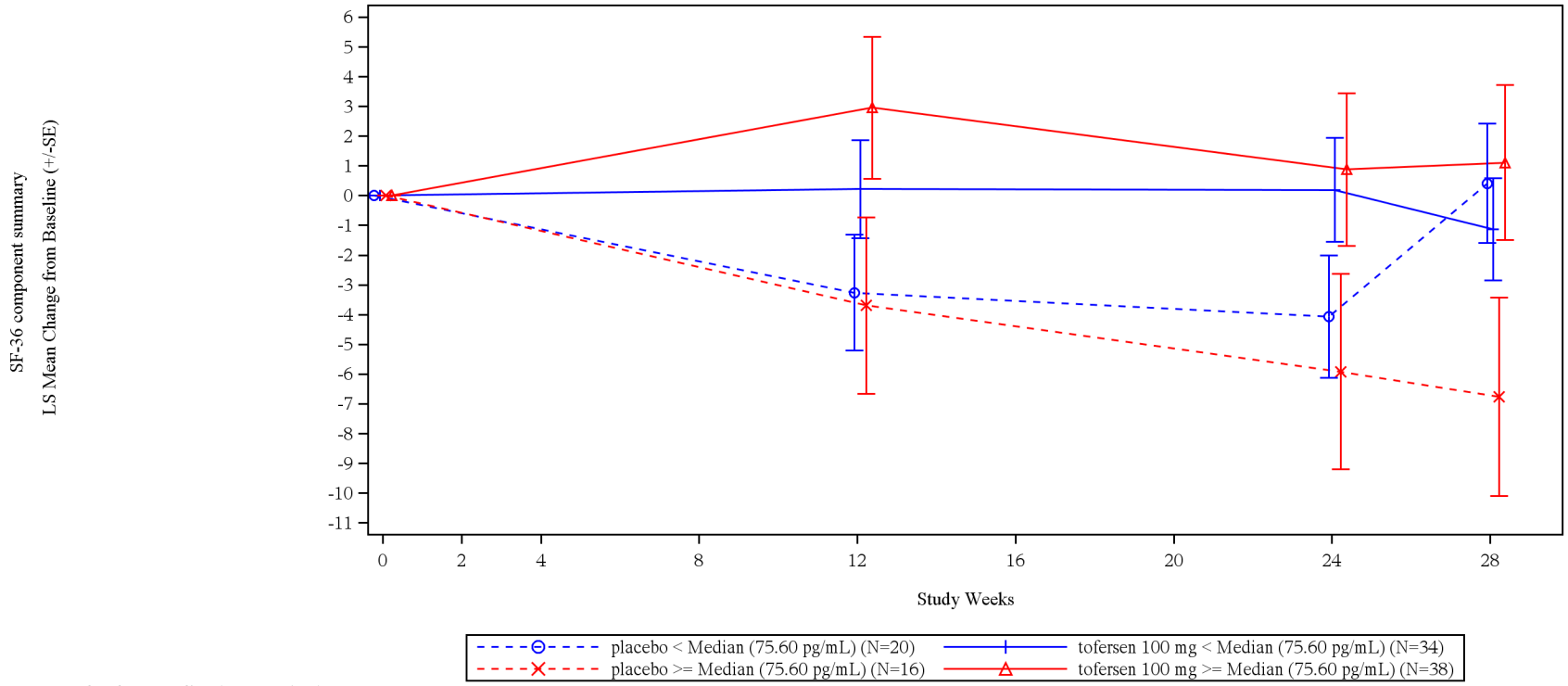
Physical Component Summary/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	12 (92.3)	20 (76.9)
Number of imputed values per imputation	1 (7.7)	6 (23.1)
LS mean change from baseline	-4.1	-3.0
SE	2.21	1.72
95% CI	(-8.39, 0.27)	(-6.37, 0.38)
LS mean difference (tofersen - placebo)		1.1
SE		2.48
95% CI		(-3.79, 5.93)
p-value		0.6671
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.21, 1.25)
p-value		0.1628

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; NE = not estimable.
Source: biib067/valueaccess/amnog/t-cf-exp-sf36-anc-mi-sgrp.sas:t-cf-exp-sf36-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

Mental Component Summary



placebo < Median (75.60 pg/mL) n=	20	20	20	18
tofersen 100 mg < Median (75.60 pg/mL) n=	34	33	30	29
placebo >= Median (75.60 pg/mL) n=	16	16	12	13
tofersen 100 mg >= Median (75.60 pg/mL) n=	38	34	33	32

Footnotes are displayed on last page.

Source: biib067/233as101-partc/csr/f-cf-phoc-sf36-anc-bpnfl-md-up.sas **Run Date:** 11NOV2021

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

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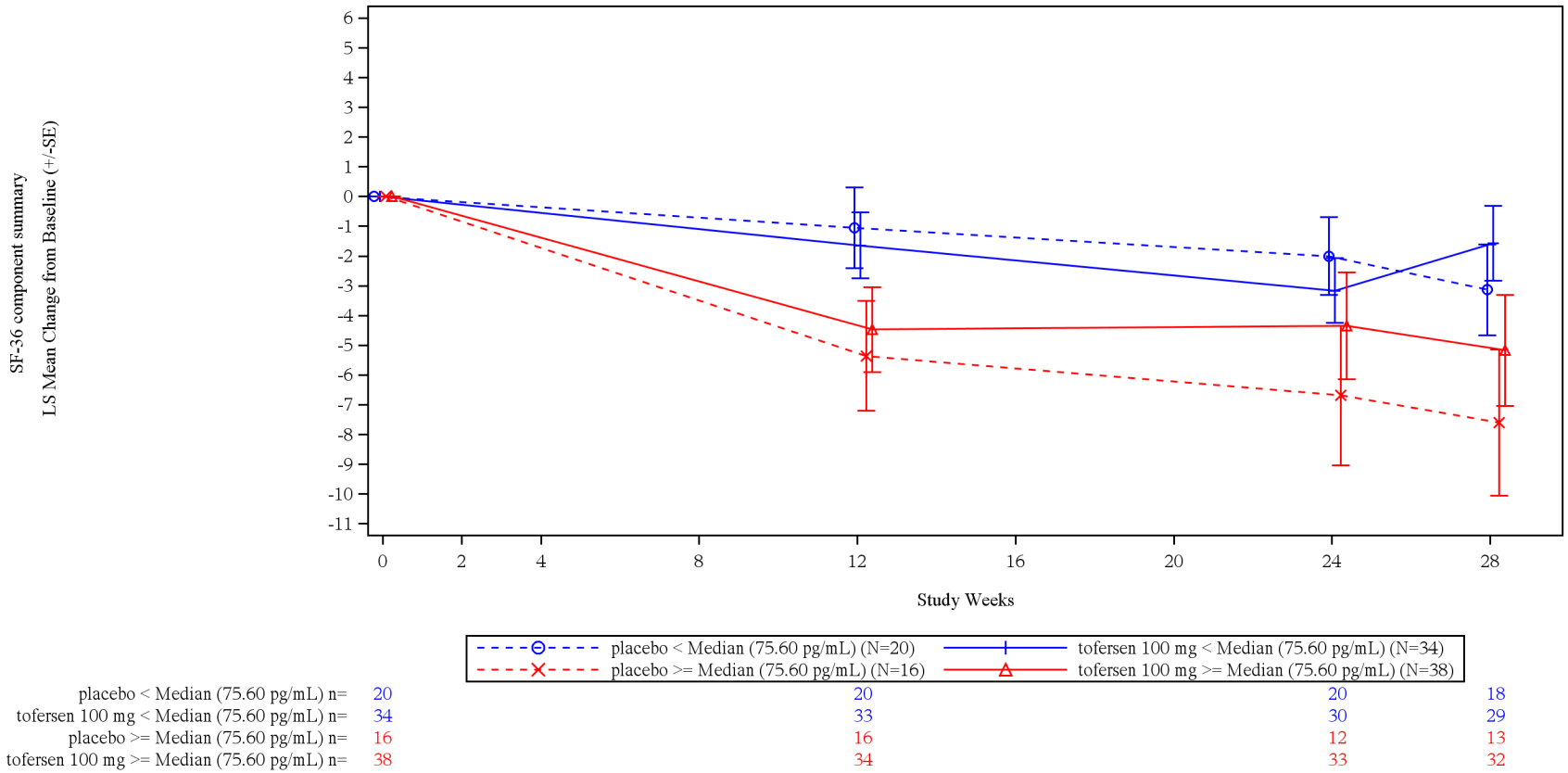
Physical Component Summary



placebo < Median (75.60 pg/mL) n=	20	20	20	18
tofersen 100 mg < Median (75.60 pg/mL) n=	34	33	30	29
placebo >= Median (75.60 pg/mL) n=	16	16	12	13
tofersen 100 mg >= Median (75.60 pg/mL) n=	38	34	33	32

Footnotes are displayed on last page.

Source: biib067/233as101-partc/csr/f-cf-phoc-sf36-anc-bpnfl-md-up.sas **Run Date:** 11NOV2021

233AS101 Part C: Line plot of SF-36 component summary LS mean change from baseline values +/- SE by visit from ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value. Multiple imputation is used for missing data.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline SF-36 component summary, and use of riluzole or edaravone.
NOTE 4: Data inadvertently collected for some subjects at Day 57, 113 and 141 for SF-36 are not analyzed unless a record falls into the visit windows for Day 85 or Day 169 and there are no data collected at the regular scheduled visit.
NOTE 5: The table at the bottom presents the number of subjects with observed non-missing data at each visit.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/233as101-partc/csr/f-cf-phoc-sf36-anc-bpnfl-md-up.sas **Run Date:** 11NOV2021

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI: treatment by subgroup interaction - ITT population

Page: 1 of 2

Mental Component Summary

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.9783	0.9569	0.9888
Baseline disease duration since symptom onset by median	0.6148	0.6035	0.4932
Baseline NfL plasma level by median	0.6727	0.5449	0.6358
Riluzole or edaravone use	0.3406	0.3323	0.3073
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.5533	0.5181	0.4443
Age at first dose (<55, >=55)	0.4687	0.4913	0.6838

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.

NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.

NOTE 4: Worsening in mental component summary is defined as change from baseline < -9.6 and worsening in physical component summary is defined as change from baseline < -9.4.

Abbreviations: SF-36 = 36 Item Short Form Health Survey.

Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 14MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI: treatment by subgroup interaction - ITT population

Physical Component Summary

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.4235	0.3669	0.2227
Baseline disease duration since symptom onset by median	0.1501	0.1292	0.1893
Baseline NfL plasma level by median	0.7551	0.7950	0.9606
Riluzole or edaravone use	0.7188	0.8341	0.8838
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3074	0.3625	0.5938
Age at first dose (<55, >=55)	0.5070	0.5106	0.6201

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
NOTE 4: Worsening in mental component summary is defined as change from baseline < -9.6 and worsening in physical component summary is defined as change from baseline < -9.4.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 14MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by gender - ITT population

Page: 1 of 4

Mental Component Summary/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	23.6	17.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.80
SE of log(RR)		0.626
95% CI		(0.234, 2.720)
p-value		0.7174
Adjusted OR - Odds Ratio (tofersen/placebo)		0.77
SE of log(OR)		0.753
95% CI		(0.175, 3.356)
p-value		0.7244
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.128
95% CI		(-0.315, 0.186)
p-value		0.6117

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by gender - ITT population

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Mental Component Summary/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	21.7	15.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.78
SE of log(RR)		0.645
95% CI		(0.220, 2.753)
p-value		0.6970
Adjusted OR - Odds Ratio (tofersen/placebo)		0.72
SE of log(OR)		0.815
95% CI		(0.146, 3.567)
p-value		0.6896
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.118
95% CI		(-0.294, 0.169)
p-value		0.5968

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by gender - ITT population

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Physical Component Summary/Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	20.7	25.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.04
SE of log(RR)		0.583
95% CI		(0.330, 3.249)
p-value		0.9514
Adjusted OR - Odds Ratio (tofersen/placebo)		1.05
SE of log(OR)		0.751
95% CI		(0.241, 4.585)
p-value		0.9468
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.133
95% CI		(-0.215, 0.307)
p-value		0.7288

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by gender - ITT population

Physical Component Summary/Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	33.1	15.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.57
SE of log(RR)		0.468
95% CI		(0.227, 1.421)
p-value		0.2265
Adjusted OR - Odds Ratio (tofersen/placebo)		0.39
SE of log(OR)		0.794
95% CI		(0.082, 1.849)
p-value		0.2357
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.18
SE of ARR		0.125
95% CI		(-0.424, 0.068)
p-value		0.1566

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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Mental Component Summary/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	14.1	14.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.24
SE of log(RR)		0.924
95% CI		(0.202, 7.601)
p-value		0.8156
Adjusted OR - Odds Ratio (tofersen/placebo)		1.27
SE of log(OR)		1.052
95% CI		(0.161, 10.010)
p-value		0.8197
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.120
95% CI		(-0.229, 0.242)
p-value		0.9572

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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Mental Component Summary/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	28.7	17.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.72
SE of log(RR)		0.589
95% CI		(0.226, 2.273)
p-value		0.5714
Adjusted OR - Odds Ratio (tofersen/placebo)		0.66
SE of log(OR)		0.701
95% CI		(0.167, 2.612)
p-value		0.5548
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.121
95% CI		(-0.347, 0.127)
p-value		0.3629

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

Physical Component Summary/< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	28.4	31.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.23
SE of log(RR)		0.486
95% CI		(0.476, 3.201)
p-value		0.6652
Adjusted OR - Odds Ratio (tofersen/placebo)		1.37
SE of log(OR)		0.723
95% CI		(0.333, 5.670)
p-value		0.6596
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.145
95% CI		(-0.252, 0.316)
p-value		0.8243

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
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233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

Physical Component Summary/>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	26.5	5.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.21
SE of log(RR)		1.101
95% CI		(0.025, 1.860)
p-value		0.1624
Adjusted OR - Odds Ratio (tofersen/placebo)		0.19
SE of log(OR)		1.068
95% CI		(0.023, 1.540)
p-value		0.1197
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.21
SE of ARR		0.109
95% CI		(-0.421, 0.006)
p-value		0.0569

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
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233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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Mental Component Summary/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	15.1	11.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.75
SE of log(RR)		0.886
95% CI		(0.132, 4.263)
p-value		0.7466
Adjusted OR - Odds Ratio (tofersen/placebo)		0.75
SE of log(OR)		0.871
95% CI		(0.136, 4.144)
p-value		0.7424
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.100
95% CI		(-0.230, 0.160)
p-value		0.7243

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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Mental Component Summary/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	32.0	20.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.48
SE of log(RR)		0.567
95% CI		(0.159, 1.466)
p-value		0.1986
Adjusted OR - Odds Ratio (tofersen/placebo)		0.37
SE of log(OR)		0.792
95% CI		(0.078, 1.743)
p-value		0.2083
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.144
95% CI		(-0.400, 0.164)
p-value		0.4126

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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Physical Component Summary/< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	20.4	10.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.67
SE of log(RR)		0.715
95% CI		(0.166, 2.730)
p-value		0.5786
Adjusted OR - Odds Ratio (tofersen/placebo)		0.62
SE of log(OR)		0.858
95% CI		(0.116, 3.353)
p-value		0.5824
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.107
95% CI		(-0.306, 0.112)
p-value		0.3647

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
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233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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Physical Component Summary/>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	35.9	27.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.88
SE of log(RR)		0.493
95% CI		(0.335, 2.320)
p-value		0.7991
Adjusted OR - Odds Ratio (tofersen/placebo)		0.83
SE of log(OR)		0.698
95% CI		(0.212, 3.269)
p-value		0.7924
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.148
95% CI		(-0.378, 0.202)
p-value		0.5533

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
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233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by riluzole or edaravone use - ITT population

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Mental Component Summary/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	16.3	17.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.07
SE of log(RR)		0.611
95% CI		(0.322, 3.537)
p-value		0.9151
Adjusted OR - Odds Ratio (tofersen/placebo)		1.08
SE of log(OR)		0.737
95% CI		(0.254, 4.580)
p-value		0.9176
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.100
95% CI		(-0.190, 0.203)
p-value		0.9457

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.

Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by riluzole or edaravone use - ITT population

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Mental Component Summary/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	32.5	14.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.44
SE of log(RR)		0.699
95% CI		(0.112, 1.741)
p-value		0.2429
Adjusted OR - Odds Ratio (tofersen/placebo)		0.36
SE of log(OR)		0.855
95% CI		(0.068, 1.939)
p-value		0.2356
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.18
SE of ARR		0.152
95% CI		(-0.476, 0.120)
p-value		0.2412

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.

Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by riluzole or edaravone use - ITT population

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Physical Component Summary/Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	25.5	16.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.67
SE of log(RR)		0.510
95% CI		(0.246, 1.814)
p-value		0.4286
Adjusted OR - Odds Ratio (tofersen/placebo)		0.60
SE of log(OR)		0.650
95% CI		(0.169, 2.159)
p-value		0.4372
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.112
95% CI		(-0.308, 0.130)
p-value		0.4267

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.

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233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by riluzole or edaravone use - ITT population

Physical Component Summary/Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in SF-36 PCS > = 9.4	30.0	23.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.87
SE of log(RR)		0.502
95% CI		(0.324, 2.320)
p-value		0.7754
Adjusted OR - Odds Ratio (tofersen/placebo)		0.77
SE of log(OR)		0.954
95% CI		(0.119, 4.997)
p-value		0.7840
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.06
SE of ARR		0.156
95% CI		(-0.366, 0.245)
p-value		0.6968

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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Mental Component Summary/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	29.1	17.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.60
SE of log(RR)		0.541
95% CI		(0.207, 1.732)
p-value		0.3446
Adjusted OR - Odds Ratio (tofersen/placebo)		0.52
SE of log(OR)		0.688
95% CI		(0.136, 2.014)
p-value		0.3458
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.125
95% CI		(-0.362, 0.128)
p-value		0.3509

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.

Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Mental Component Summary/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	13.4	14.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.08
SE of log(RR)		0.832
95% CI		(0.212, 5.525)
p-value		0.9254
Adjusted OR - Odds Ratio (tofersen/placebo)		1.09
SE of log(OR)		0.901
95% CI		(0.186, 6.370)
p-value		0.9246
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.110
95% CI		(-0.204, 0.226)
p-value		0.9216

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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Physical Component Summary/mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	34.5	31.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.93
SE of log(RR)		0.392
95% CI		(0.431, 2.001)
p-value		0.8492
Adjusted OR - Odds Ratio (tofersen/placebo)		0.89
SE of log(OR)		0.613
95% CI		(0.268, 2.970)
p-value		0.8531
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.133
95% CI		(-0.289, 0.231)
p-value		0.8264

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Physical Component Summary/Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	17.1	4.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.28
SE of log(RR)		1.116
95% CI		(0.031, 2.455)
p-value		0.2478
Adjusted OR - Odds Ratio (tofersen/placebo)		0.27
SE of log(OR)		1.170
95% CI		(0.027, 2.628)
p-value		0.2567
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.111
95% CI		(-0.340, 0.096)
p-value		0.2719

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by age at first dose - ITT population

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Mental Component Summary/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	19.8	10.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.48
SE of log(RR)		0.623
95% CI		(0.142, 1.639)
p-value		0.2431
Adjusted OR - Odds Ratio (tofersen/placebo)		0.42
SE of log(OR)		0.762
95% CI		(0.095, 1.880)
p-value		0.2577
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.099
95% CI		(-0.286, 0.102)
p-value		0.3524

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by age at first dose - ITT population

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Mental Component Summary/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in SF-36 MCS > = 9.6	27.5	25.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.96
SE of log(RR)		0.719
95% CI		(0.233, 3.907)
p-value		0.9490
Adjusted OR - Odds Ratio (tofersen/placebo)		0.95
SE of log(OR)		0.919
95% CI		(0.157, 5.764)
p-value		0.9563
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.158
95% CI		(-0.327, 0.294)
p-value		0.9167

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by age at first dose - ITT population

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Physical Component Summary/< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	24.9	20.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.70
SE of log(RR)		0.511
95% CI		(0.259, 1.914)
p-value		0.4911
Adjusted OR - Odds Ratio (tofersen/placebo)		0.63
SE of log(OR)		0.665
95% CI		(0.171, 2.322)
p-value		0.4881
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.04
SE of ARR		0.112
95% CI		(-0.265, 0.175)
p-value		0.6897

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of worsening in SF-36 component summary at Week 28 using MI by age at first dose - ITT population

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Physical Component Summary/>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	31.5	17.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.19
SE of log(RR)		0.608
95% CI		(0.362, 3.930)
p-value		0.7725
Adjusted OR - Odds Ratio (tofersen/placebo)		1.43
SE of log(OR)		1.051
95% CI		(0.182, 11.235)
p-value		0.7333
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.14
SE of ARR		0.154
95% CI		(-0.442, 0.163)
p-value		0.3660

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-wor-wk28-sgrp.sas:t-cf-sf36-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 15MAR2023

233AS101 Part C: Summary of proportion of improvement in SF-36 component summary at Week 28 using MI: treatment by subgroup interaction – ITT population

Subgroup analyses not performed. Condition of having at least 10 events in at least one of the subgroup categories for binary endpoint is not met.

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.7931
Baseline disease duration since symptom onset by median	0.2856
Baseline NfL plasma level by median	0.1078
Riluzole or edaravone use	0.0709
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.0645
Age at first dose (<55, >=55)	0.6852

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline WPAI-Q6, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed. The analysis is based on the combined MI datasets from the mITT and non mITT populations.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 16FEB2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
Number of observations per imputation	15 (88.2)	22 (75.9)
Number of imputed values per imputation	2 (11.8)	7 (24.1)
LS mean change from baseline	0.8	0.7
SE	0.52	0.43
95% CI	(-0.21, 1.85)	(-0.14, 1.54)
LS mean difference (tofersen - placebo)		-0.1
SE		0.63
95% CI		(-1.35, 1.12)
p-value		0.8520
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.93, 0.39)
p-value		0.4149

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
Number of observations per imputation	15 (78.9)	38 (88.4)
Number of imputed values per imputation	4 (21.1)	5 (11.6)
LS mean change from baseline	0.1	0.4
SE	0.69	0.56
95% CI	(-1.25, 1.47)	(-0.66, 1.55)
LS mean difference (tofersen - placebo)		0.3
SE		0.67
95% CI		(-0.98, 1.65)
p-value		0.6222
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.48, 0.72)
p-value		0.6923

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline disease duration since symptom onset, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	13 (86.7)	33 (86.8)
Number of imputed values per imputation	2 (13.3)	5 (13.2)
LS mean change from baseline	1.1	0.8
SE	0.65	0.52
95% CI	(-0.15, 2.40)	(-0.18, 1.84)
LS mean difference (tofersen - placebo)		-0.3
SE		0.65
95% CI		(-1.58, 0.98)
p-value		0.6461
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.71, 0.58)
p-value		0.8445

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by baseline disease duration since symptom onset (median) - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	17 (81.0)	27 (79.4)
Number of imputed values per imputation	4 (19.0)	7 (20.6)
LS mean change from baseline	0.1	0.8
SE	0.59	0.48
95% CI	(-1.05, 1.24)	(-0.09, 1.78)
LS mean difference (tofersen - placebo)		0.7
SE		0.70
95% CI		(-0.62, 2.12)
p-value		0.2827
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.61, 0.60)
p-value		0.9915

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
Number of observations per imputation	18 (90.0)	29 (85.3)
Number of imputed values per imputation	2 (10.0)	5 (14.7)
LS mean change from baseline	0.0	0.6
SE	0.51	0.43
95% CI	(-1.02, 0.96)	(-0.22, 1.47)
LS mean difference (tofersen - placebo)		0.7
SE		0.62
95% CI		(-0.55, 1.86)
p-value		0.2873
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.51, 0.67)
p-value		0.7943

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
Number of observations per imputation	12 (75.0)	31 (81.6)
Number of imputed values per imputation	4 (25.0)	7 (18.4)
LS mean change from baseline	1.5	0.8
SE	0.63	0.50
95% CI	(0.27, 2.76)	(-0.14, 1.82)
LS mean difference (tofersen - placebo)		-0.7
SE		0.64
95% CI		(-1.92, 0.57)
p-value		0.2885
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.83, 0.50)
p-value		0.6307

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
Number of observations per imputation	19 (86.4)	41 (91.1)
Number of imputed values per imputation	3 (13.6)	4 (8.9)
LS mean change from baseline	0.1	0.9
SE	0.45	0.31
95% CI	(-0.76, 1.01)	(0.33, 1.55)
LS mean difference (tofersen - placebo)		0.8
SE		0.55
95% CI		(-0.26, 1.90)
p-value		0.1361
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.31, 0.78)
p-value		0.4054

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, and baseline WPAI-Q6. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
Number of observations per imputation	11 (78.6)	19 (70.4)
Number of imputed values per imputation	3 (21.4)	8 (29.6)
LS mean change from baseline	1.2	0.4
SE	0.65	0.49
95% CI	(-0.10, 2.47)	(-0.58, 1.35)
LS mean difference (tofersen - placebo)		-0.8
SE		0.81
95% CI		(-2.40, 0.79)
p-value		0.3238
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-1.11, 0.39)
p-value		0.3485

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, and baseline WPAI-Q6. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
Number of observations per imputation	18 (85.7)	32 (82.1)
Number of imputed values per imputation	3 (14.3)	7 (17.9)
LS mean change from baseline	1.2	0.8
SE	0.59	0.51
95% CI	(0.06, 2.37)	(-0.16, 1.83)
LS mean difference (tofersen - placebo)		-0.4
SE		0.58
95% CI		(-1.52, 0.75)
p-value		0.5083
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.83, 0.33)
p-value		0.3988

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
Number of observations per imputation	12 (80.0)	28 (84.8)
Number of imputed values per imputation	3 (20.0)	5 (15.2)
LS mean change from baseline	-0.4	0.9
SE	0.64	0.47
95% CI	(-1.64, 0.88)	(-0.04, 1.79)
LS mean difference (tofersen - placebo)		1.3
SE		0.75
95% CI		(-0.22, 2.72)
p-value		0.0945
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.42, 0.94)
p-value		0.4510

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
Number of observations per imputation	19 (82.6)	41 (89.1)
Number of imputed values per imputation	4 (17.4)	5 (10.9)
LS mean change from baseline	0.5	0.6
SE	0.57	0.43
95% CI	(-0.66, 1.57)	(-0.28, 1.42)
LS mean difference (tofersen - placebo)		0.1
SE		0.61
95% CI		(-1.08, 1.31)
p-value		0.8516
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.55, 0.53)
p-value		0.9690

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: WPAI-Q6 change from baseline at week 28 ANCOVA analysis using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
Number of observations per imputation	11 (84.6)	19 (73.1)
Number of imputed values per imputation	2 (15.4)	7 (26.9)
LS mean change from baseline	0.6	1.3
SE	0.66	0.54
95% CI	(-0.65, 1.93)	(0.22, 2.34)
LS mean difference (tofersen - placebo)		0.6
SE		0.73
95% CI		(-0.79, 2.08)
p-value		0.3797
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.79, 0.70)
p-value		0.9040

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-exp-wpai-anc-mi-sgrp.sas:t-cf-exp-wpai-anc-mi-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21MAR2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI: treatment by subgroup interaction - ITT population

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Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.1526	0.1557	0.1886
Baseline disease duration since symptom onset by median	0.9823	0.9634	0.8873
Baseline NfL plasma level by median	0.4210	0.3436	0.3591
Riluzole or edaravone use	0.5675	0.5668	0.5527
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.3764	0.3641	0.3424
Age at first dose (<55, >=55)	0.6174	0.6109	0.3554

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 19JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	39.4	25.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.60
SE of log(RR)		0.470
95% CI		(0.240, 1.514)
p-value		0.2808
Adjusted OR - Odds Ratio (tofersen/placebo)		0.47
SE of log(OR)		0.723
95% CI		(0.113, 1.927)
p-value		0.2927
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.14
SE of ARR		0.150
95% CI		(-0.436, 0.150)
p-value		0.3388

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	25.0	36.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.51
SE of log(RR)		0.448
95% CI		(0.630, 3.643)
p-value		0.3534
Adjusted OR - Odds Ratio (tofersen/placebo)		1.83
SE of log(OR)		0.641
95% CI		(0.521, 6.438)
p-value		0.3456
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.128
95% CI		(-0.137, 0.366)
p-value		0.3724

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	34.2	35.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.06
SE of log(RR)		0.441
95% CI		(0.446, 2.514)
p-value		0.8979
Adjusted OR - Odds Ratio (tofersen/placebo)		1.10
SE of log(OR)		0.673
95% CI		(0.293, 4.098)
p-value		0.8919
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.149
95% CI		(-0.283, 0.301)
p-value		0.9495

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by baseline disease duration since symptom onset (median) - ITT population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	30.0	28.2
Adjusted RR - Relative Risk (tofersen/placebo)		1.04
SE of log(RR)		0.515
95% CI		(0.380, 2.860)
p-value		0.9357
Adjusted OR - Odds Ratio (tofersen/placebo)		1.05
SE of log(OR)		0.656
95% CI		(0.290, 3.798)
p-value		0.9414
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.134
95% CI		(-0.281, 0.243)
p-value		0.8871

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	15.8	22.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.47
SE of log(RR)		0.790
95% CI		(0.314, 6.937)
p-value		0.6228
Adjusted OR - Odds Ratio (tofersen/placebo)		1.49
SE of log(OR)		0.755
95% CI		(0.339, 6.543)
p-value		0.5986
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.112
95% CI		(-0.155, 0.285)
p-value		0.5649

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by baseline plasma NfL level (median) - ITT population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	51.8	40.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.341
95% CI		(0.378, 1.441)
p-value		0.3730
Adjusted OR - Odds Ratio (tofersen/placebo)		0.58
SE of log(OR)		0.656
95% CI		(0.159, 2.088)
p-value		0.4020
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.11
SE of ARR		0.158
95% CI		(-0.423, 0.196)
p-value		0.4728

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

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Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	25.2	30.1
Adjusted RR - Relative Risk (tofersen/placebo)		1.21
SE of log(RR)		0.456
95% CI		(0.497, 2.965)
p-value		0.6711
Adjusted OR - Odds Ratio (tofersen/placebo)		1.30
SE of log(OR)		0.607
95% CI		(0.395, 4.274)
p-value		0.6659
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.118
95% CI		(-0.182, 0.281)
p-value		0.6765

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: WPAI = Work Productivity and Activity Inventor.

Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	42.2	34.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.85
SE of log(RR)		0.435
95% CI		(0.361, 1.988)
p-value		0.7023
Adjusted OR - Odds Ratio (tofersen/placebo)		0.75
SE of log(OR)		0.735
95% CI		(0.178, 3.185)
p-value		0.7004
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.171
95% CI		(-0.410, 0.262)
p-value		0.6657

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression.
Abbreviations: WPAI = Work Productivity and Activity Inventor.

Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	41.7	34.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.83
SE of log(RR)		0.355
95% CI		(0.413, 1.663)
p-value		0.5968
Adjusted OR - Odds Ratio (tofersen/placebo)		0.74
SE of log(OR)		0.584
95% CI		(0.235, 2.314)
p-value		0.6015
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.07
SE of ARR		0.137
95% CI		(-0.343, 0.196)
p-value		0.5921

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by prognostic enrichment criteria for rapid disease progression - ITT population

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Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	18.0	29.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.65
SE of log(RR)		0.688
95% CI		(0.428, 6.340)
p-value		0.4680
Adjusted OR - Odds Ratio (tofersen/placebo)		1.86
SE of log(OR)		0.836
95% CI		(0.362, 9.600)
p-value		0.4564
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.135
95% CI		(-0.155, 0.375)
p-value		0.4160

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.

Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	29.7	36.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.17
SE of log(RR)		0.391
95% CI		(0.546, 2.523)
p-value		0.6823
Adjusted OR - Odds Ratio (tofersen/placebo)		1.26
SE of log(OR)		0.573
95% CI		(0.410, 3.877)
p-value		0.6853
ARR - Absolute Risk Reduction (tofersen - placebo)		0.07
SE of ARR		0.123
95% CI		(-0.172, 0.312)
p-value		0.5720

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with worsening in WPAI-16 score > = 15%	35.5	23.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.76
SE of log(RR)		0.785
95% CI		(0.162, 3.519)
p-value		0.7206
Adjusted OR - Odds Ratio (tofersen/placebo)		0.71
SE of log(OR)		0.953
95% CI		(0.110, 4.630)
p-value		0.7242
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.12
SE of ARR		0.166
95% CI		(-0.447, 0.204)
p-value		0.4639

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpai-wor-wk28-sgrp.sas:t-cf-wpai-wor-wk28-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 21JUN2023

233AS101 Part C: Summary of proportion of improvement in WPAI-Q6 >= 15% at Week 28 using MI by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Average proportion of subjects with improvement in WPAI-Q6 score > = 15%	13.3	19.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.65
SE of log(RR)		0.676
95% CI		(0.438, 6.213)
p-value		0.4593
Adjusted OR - Odds Ratio (tofersen/placebo)		1.74
SE of log(OR)		0.737
95% CI		(0.409, 7.358)
p-value		0.4546
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.095
95% CI		(-0.130, 0.243)
p-value		0.5541

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propim-byvis-itt-sgrp.sas:t-cf-wpa-propim-byvis-itt-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: Summary of proportion of improvement in WPAI-Q6 >= 15% at Week 28 using MI by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Average proportion of subjects with improvement in WPAI-Q6 score > = 15%	9.8	4.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.54
SE of log(RR)		1.132
95% CI		(0.058, 4.953)
p-value		0.5826
Adjusted OR - Odds Ratio (tofersen/placebo)		0.50
SE of log(OR)		1.317
95% CI		(0.037, 6.573)
p-value		0.5947
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.05
SE of ARR		0.107
95% CI		(-0.263, 0.156)
p-value		0.6168

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for prognostic enrichment criteria for rapid disease progression and riluzole or edaravone use.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propim-byvis-itt-sgrp.sas:t-cf-wpa-propim-byvis-itt-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30JUN2023

233AS101 Part C: Summary of proportion of improvement in WPAI-Q6 by 15% at week 28 using MI: treatment by subgroup interaction

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Subgroup	p-Value Based on adjusted RR for Treatment by Subgroup Interaction	p-Value Based on adjusted OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	NA	NA	NA
Baseline disease duration since symptom onset by median	NA	NA	NA
Baseline NfL plasma level by median	NA	NA	NA
Riluzole or edaravone use	NA	NA	NA
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	0.3936	0.4061	0.4417

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: NA is presented for the subgroups without at least 10 events occurred in at least one of the subgroup categories.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propim-itt-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JUN2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) treatment by subgroup interaction - ITT population

Suicidal ideation (1-5)

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.3417	0.3346	0.2900
Baseline disease duration since symptom onset by median	0.5928	0.5894	0.5626
Baseline NfL plasma level by median	0.6736	0.6725	0.7187
Riluzole or edaravone use	0.5044	0.5036	0.5924
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	0.8034	0.8055	0.8381

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
NOTE 4: The interaction test is not conducted for any subgroup that has at least one category with no events.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-int-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) treatment by subgroup interaction - ITT population

(1) Wish to be dead

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.8966	0.8858	0.6986
Baseline disease duration since symptom onset by median	0.8122	0.8170	0.9311
Baseline NfL plasma level by median	0.8565	0.8616	0.9766
Riluzole or edaravone use	0.9852	0.9731	0.7733
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	0.6217	0.6160	0.5320

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
NOTE 4: The interaction test is not conducted for any subgroup that has at least one category with no events.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-int-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) treatment by subgroup interaction - ITT population

(2) Non-specific active suicidal thoughts

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.3063	0.3082	0.4417
Baseline disease duration since symptom onset by median	0.5071	0.5116	0.6700
Baseline NfL plasma level by median	NA	NA	NA
Riluzole or edaravone use	0.3797	0.3669	0.2802
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	NA	NA	NA
Age at first dose (<55, >=55)	0.3797	0.3752	0.3806

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
NOTE 4: The interaction test is not conducted for any subgroup that has at least one category with no events.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-int-itt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

Suicidal Ideation (1-5),Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with answer = YES	1 (5.9)	4 (13.8)
RR - Relative Risk (tofersen/placebo)		2.34
SE of log (RR)		1.075
95% CI		(0.285, 19.301)
p-value		0.4281
OR - Odds Ratio (tofersen/placebo)		2.56
SE of log (OR)		1.163
95% CI		(0.262, 25.013)
p-value		0.4189
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.086
95% CI		(-0.089, 0.247)
p-value		0.3564

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

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Suicidal Ideation (1-5),Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with answer = YES	1 (5.3)	1 (2.3)
RR - Relative Risk (tofersen/placebo)		0.44
SE of log (RR)		1.387
95% CI		(0.029, 6.699)
p-value		0.5560
OR - Odds Ratio (tofersen/placebo)		0.43
SE of log (OR)		1.442
95% CI		(0.025, 7.235)
p-value		0.5568
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.056
95% CI		(-0.139, 0.081)
p-value		0.6008

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

(1) Wish to be dead,Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with answer = YES	1 (5.9)	3 (10.3)
RR - Relative Risk (tofersen/placebo)		1.76
SE of log (RR)		1.114
95% CI		(0.198, 15.597)
p-value		0.6122
OR - Odds Ratio (tofersen/placebo)		1.85
SE of log (OR)		1.198
95% CI		(0.177, 19.306)
p-value		0.6087
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.080
95% CI		(-0.113, 0.202)
p-value		0.5786

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

(1) Wish to be dead,Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.36
SE of log (RR)		1.611
95% CI		(0.058, 32.035)
p-value		0.8473
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		1.656
95% CI		(0.054, 35.329)
p-value		0.8470
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.044
95% CI		(-0.078, 0.096)
p-value		0.8376

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

(2) Non-specific active suicidal thoughts,Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with answer = YES	1 (5.9)	2 (6.9)
RR - Relative Risk (tofersen/placebo)		1.17
SE of log (RR)		1.186
95% CI		(0.115, 11.985)
p-value		0.8933
OR - Odds Ratio (tofersen/placebo)		1.19
SE of log (OR)		1.265
95% CI		(0.099, 14.136)
p-value		0.8931
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.074
95% CI		(-0.135, 0.155)
p-value		0.8909

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

(2) Non-specific active suicidal thoughts,Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		0.15
SE of log (RR)		1.611
95% CI		(0.006, 3.559)
p-value		0.2413
OR - Odds Ratio (tofersen/placebo)		0.14
SE of log (OR)		1.656
95% CI		(0.006, 3.643)
p-value		0.2382
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.061
95% CI		(-0.183, 0.056)
p-value		0.2970

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by gender - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.80
SE of log (RR)		1.606
95% CI		(0.077, 41.871)
p-value		0.7143
OR - Odds Ratio (tofersen/placebo)		1.84
SE of log (OR)		1.661
95% CI		(0.071, 47.770)
p-value		0.7130
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.056
95% CI		(-0.087, 0.131)
p-value		0.6890

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.

NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.

Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

Suicidal Ideation (1-5),< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	1 (6.7)	4 (10.5)
RR - Relative Risk (tofersen/placebo)		1.58
SE of log (RR)		1.076
95% CI		(0.192, 13.001)
p-value		0.6711
OR - Odds Ratio (tofersen/placebo)		1.65
SE of log (OR)		1.162
95% CI		(0.169, 16.070)
p-value		0.6677
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.081
95% CI		(-0.121, 0.198)
p-value		0.6354

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

Suicidal Ideation (1-5),>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with answer = YES	1 (4.8)	1 (2.9)
RR - Relative Risk (tofersen/placebo)		0.62
SE of log (RR)		1.387
95% CI		(0.041, 9.356)
p-value		0.7282
OR - Odds Ratio (tofersen/placebo)		0.61
SE of log (OR)		1.442
95% CI		(0.036, 10.238)
p-value		0.7284
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.02
SE of ARR		0.055
95% CI		(-0.126, 0.089)
p-value		0.7395

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

(1) Wish to be dead,< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	1 (6.7)	3 (7.9)
RR - Relative Risk (tofersen/placebo)		1.18
SE of log (RR)		1.114
95% CI		(0.133, 10.506)
p-value		0.8793
OR - Odds Ratio (tofersen/placebo)		1.20
SE of log (OR)		1.197
95% CI		(0.115, 12.539)
p-value		0.8790
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.078
95% CI		(-0.140, 0.165)
p-value		0.8747

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

(1) Wish to be dead,>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.89
SE of log (RR)		1.610
95% CI		(0.080, 44.264)
p-value		0.6936
OR - Odds Ratio (tofersen/placebo)		1.93
SE of log (OR)		1.656
95% CI		(0.075, 49.463)
p-value		0.6924
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.047
95% CI		(-0.071, 0.112)
p-value		0.6665

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

(2) Non-specific active suicidal thoughts,< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	1 (6.7)	2 (5.3)
RR - Relative Risk (tofersen/placebo)		0.79
SE of log (RR)		1.186
95% CI		(0.077, 8.073)
p-value		0.8420
OR - Odds Ratio (tofersen/placebo)		0.78
SE of log (OR)		1.265
95% CI		(0.065, 9.274)
p-value		0.8425
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.074
95% CI		(-0.159, 0.131)
p-value		0.8494

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

(2) Non-specific active suicidal thoughts,>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		0.21
SE of log (RR)		1.610
95% CI		(0.009, 4.918)
p-value		0.3317
OR - Odds Ratio (tofersen/placebo)		0.20
SE of log (OR)		1.657
95% CI		(0.008, 5.093)
p-value		0.3284
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.05
SE of ARR		0.057
95% CI		(-0.166, 0.059)
p-value		0.3474

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline disease duration since symptom onset (median) - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.23
SE of log (RR)		1.606
95% CI		(0.053, 28.643)
p-value		0.8971
OR - Odds Ratio (tofersen/placebo)		1.24
SE of log (OR)		1.661
95% CI		(0.048, 32.136)
p-value		0.8969
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.053
95% CI		(-0.097, 0.112)
p-value		0.8924

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

Suicidal Ideation (1-5),< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.80
SE of log (RR)		1.609
95% CI		(0.077, 42.197)
p-value		0.7150
OR - Odds Ratio (tofersen/placebo)		1.84
SE of log (OR)		1.657
95% CI		(0.071, 47.226)
p-value		0.7139
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.048
95% CI		(-0.075, 0.113)
p-value		0.6899

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

Suicidal Ideation (1-5),>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	2 (12.5)	4 (10.5)
RR - Relative Risk (tofersen/placebo)		0.84
SE of log (RR)		0.813
95% CI		(0.171, 4.145)
p-value		0.8326
OR - Odds Ratio (tofersen/placebo)		0.82
SE of log (OR)		0.922
95% CI		(0.135, 5.022)
p-value		0.8333
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.02
SE of ARR		0.097
95% CI		(-0.209, 0.169)
p-value		0.8380

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

(1) Wish to be dead,< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.80
SE of log (RR)		1.609
95% CI		(0.077, 42.197)
p-value		0.7150
OR - Odds Ratio (tofersen/placebo)		1.84
SE of log (OR)		1.657
95% CI		(0.071, 47.226)
p-value		0.7139
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.048
95% CI		(-0.075, 0.113)
p-value		0.6899

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

(1) Wish to be dead,>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	1 (6.3)	3 (7.9)
RR - Relative Risk (tofersen/placebo)		1.26
SE of log (RR)		1.116
95% CI		(0.142, 11.247)
p-value		0.8341
OR - Odds Ratio (tofersen/placebo)		1.29
SE of log (OR)		1.195
95% CI		(0.124, 13.382)
p-value		0.8335
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.075
95% CI		(-0.130, 0.163)
p-value		0.8257

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

(2) Non-specific active suicidal thoughts,>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	2 (12.5)	2 (5.3)
RR - Relative Risk (tofersen/placebo)		0.42
SE of log (RR)		0.955
95% CI		(0.065, 2.734)
p-value		0.3648
OR - Odds Ratio (tofersen/placebo)		0.39
SE of log (OR)		1.048
95% CI		(0.050, 3.036)
p-value		0.3677
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.090
95% CI		(-0.249, 0.105)
p-value		0.4227

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by baseline plasma NfL level - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.31
SE of log (RR)		1.607
95% CI		(0.056, 30.501)
p-value		0.8674
OR - Odds Ratio (tofersen/placebo)		1.32
SE of log (OR)		1.659
95% CI		(0.051, 34.131)
p-value		0.8671
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.051
95% CI		(-0.091, 0.110)
p-value		0.8599

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

Suicidal Ideation (1-5),Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		1.528
95% CI		(0.125, 49.955)
p-value		0.5487
OR - Odds Ratio (tofersen/placebo)		2.59
SE of log (OR)		1.571
95% CI		(0.119, 56.200)
p-value		0.5452
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.045
95% CI		(-0.056, 0.121)
p-value		0.4705

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

Suicidal Ideation (1-5),Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with answer = YES	2 (14.3)	3 (11.1)
RR - Relative Risk (tofersen/placebo)		0.78
SE of log (RR)		0.851
95% CI		(0.147, 4.126)
p-value		0.7679
OR - Odds Ratio (tofersen/placebo)		0.75
SE of log (OR)		0.979
95% CI		(0.110, 5.109)
p-value		0.7689
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.111
95% CI		(-0.250, 0.187)
p-value		0.7756

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

(1) Wish to be dead,Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		1.613
95% CI		(0.064, 35.399)
p-value		0.8015
OR - Odds Ratio (tofersen/placebo)		1.52
SE of log (OR)		1.653
95% CI		(0.059, 38.751)
p-value		0.8010
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.040
95% CI		(-0.068, 0.090)
p-value		0.7865

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

(1) Wish to be dead,Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with answer = YES	1 (7.1)	3 (11.1)
RR - Relative Risk (tofersen/placebo)		1.56
SE of log (RR)		1.107
95% CI		(0.178, 13.613)
p-value		0.6897
OR - Odds Ratio (tofersen/placebo)		1.63
SE of log (OR)		1.205
95% CI		(0.153, 17.239)
p-value		0.6870
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.092
95% CI		(-0.140, 0.219)
p-value		0.6650

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

(2) Non-specific active suicidal thoughts,Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		1.613
95% CI		(0.064, 35.399)
p-value		0.8015
OR - Odds Ratio (tofersen/placebo)		1.52
SE of log (OR)		1.653
95% CI		(0.059, 38.751)
p-value		0.8010
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.040
95% CI		(-0.068, 0.090)
p-value		0.7865

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

(2) Non-specific active suicidal thoughts,Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with answer = YES	2 (14.3)	1 (3.7)
RR - Relative Risk (tofersen/placebo)		0.26
SE of log (RR)		1.180
95% CI		(0.026, 2.617)
p-value		0.2525
OR - Odds Ratio (tofersen/placebo)		0.23
SE of log (OR)		1.273
95% CI		(0.019, 2.800)
p-value		0.2496
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.100
95% CI		(-0.302, 0.091)
p-value		0.2916

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by riluzoe or edaravone use - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.61
SE of log (RR)		1.601
95% CI		(0.070, 37.078)
p-value		0.7670
OR - Odds Ratio (tofersen/placebo)		1.64
SE of log (OR)		1.665
95% CI		(0.063, 42.932)
p-value		0.7660
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.063
95% CI		(-0.103, 0.144)
p-value		0.7477

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by prognostic enrichment criteria for rapid disease progression - ITT population

Suicidal Ideation (1-5),mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with answer = YES	2 (9.5)	5 (12.8)
RR - Relative Risk (tofersen/placebo)		1.35
SE of log (RR)		0.792
95% CI		(0.285, 6.353)
p-value		0.7073
OR - Odds Ratio (tofersen/placebo)		1.40
SE of log (OR)		0.884
95% CI		(0.247, 7.906)
p-value		0.7054
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.083
95% CI		(-0.131, 0.197)
p-value		0.6929

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by prognostic enrichment criteria for rapid disease progression - ITT population

(1) Wish to be dead,mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with answer = YES	1 (4.8)	4 (10.3)
RR - Relative Risk (tofersen/placebo)		2.15
SE of log (RR)		1.085
95% CI		(0.257, 18.054)
p-value		0.4794
OR - Odds Ratio (tofersen/placebo)		2.29
SE of log (OR)		1.153
95% CI		(0.239, 21.885)
p-value		0.4732
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.067
95% CI		(-0.077, 0.187)
p-value		0.4138

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by prognostic enrichment criteria for rapid disease progression - ITT population

(2) Non-specific active suicidal thoughts,mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with answer = YES	2 (9.5)	2 (5.1)
RR - Relative Risk (tofersen/placebo)		0.54
SE of log (RR)		0.963
95% CI		(0.082, 3.553)
p-value		0.5202
OR - Odds Ratio (tofersen/placebo)		0.51
SE of log (OR)		1.039
95% CI		(0.067, 3.936)
p-value		0.5212
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.073
95% CI		(-0.187, 0.099)
p-value		0.5479

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by prognostic enrichment criteria for rapid disease progression - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.65
SE of log (RR)		1.611
95% CI		(0.070, 38.815)
p-value		0.7560
OR - Odds Ratio (tofersen/placebo)		1.68
SE of log (OR)		1.655
95% CI		(0.065, 42.941)
p-value		0.7552
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.044
95% CI		(-0.071, 0.100)
p-value		0.7355

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

Suicidal Ideation (1-5),< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with answer = YES	1 (4.3)	3 (6.5)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		1.126
95% CI		(0.165, 13.634)
p-value		0.7188
OR - Odds Ratio (tofersen/placebo)		1.53
SE of log (OR)		1.184
95% CI		(0.151, 15.630)
p-value		0.7175
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.056
95% CI		(-0.088, 0.131)
p-value		0.6978

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

Suicidal Ideation (1-5),>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with answer = YES	1 (7.7)	2 (7.7)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		1.177
95% CI		(0.100, 10.037)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		1.275
95% CI		(0.082, 12.164)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.091
95% CI		(-0.177, 0.177)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

(1) Wish to be dead,< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with answer = YES	1 (4.3)	2 (4.3)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		1.198
95% CI		(0.096, 10.461)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		1.252
95% CI		(0.086, 11.640)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.052
95% CI		(-0.102, 0.102)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

(1) Wish to be dead,>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		2.59
SE of log (RR)		1.514
95% CI		(0.133, 50.381)
p-value		0.5291
OR - Odds Ratio (tofersen/placebo)		2.76
SE of log (OR)		1.586
95% CI		(0.123, 61.661)
p-value		0.5228
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.075
95% CI		(-0.089, 0.203)
p-value		0.4461

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

(2) Non-specific active suicidal thoughts,< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with answer = YES	1 (4.3)	2 (4.3)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		1.198
95% CI		(0.096, 10.461)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		1.252
95% CI		(0.086, 11.640)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.052
95% CI		(-0.102, 0.102)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

(2) Non-specific active suicidal thoughts,>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with answer = YES	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		0.17
SE of log (RR)		1.599
95% CI		(0.008, 3.973)
p-value		0.2724
OR - Odds Ratio (tofersen/placebo)		0.16
SE of log (OR)		1.669
95% CI		(0.006, 4.139)
p-value		0.2676
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.09
SE of ARR		0.087
95% CI		(-0.258, 0.081)
p-value		0.3063

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit using last observation carried over (LOCF) by age at first dose - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act,< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.53
SE of log (RR)		1.614
95% CI		(0.065, 36.202)
p-value		0.7915
OR - Odds Ratio (tofersen/placebo)		1.55
SE of log (OR)		1.653
95% CI		(0.061, 39.528)
p-value		0.7910
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.039
95% CI		(-0.065, 0.087)
p-value		0.7753

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-wor-sgrp-itt.sas:t-cssrs-wor-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 29MAR2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data): treatment by subgroup interaction - ITT population

Page: 1 of 1

Subgroup	p-value for Treatment by Subgroup Interaction
Gender (female, male)	0.2628
Baseline disease duration since symptom onset by median	0.5670
Baseline NfL plasma level by median	0.0043
Riluzole or edaravone use	0.4231
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.1976
Age at first dose (<55, >=55)	0.8267

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.

NOTE 2: P-value is based on a ANCOVA model adjusted for baseline disease duration since symptom onset, baseline MMSE total score, riluzole or edaravone use, subgroup and treatment by subgroup interaction. The ANCOVA does not include baseline disease duration if that is the subgroup being analyzed. Similarly, use of riluzole or edaravone is not included as a covariate if that is the subgroup being analyzed.

Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance.

Source: biib067/valueaccess/amnog/t-mmse-chg-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 21JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by gender - ITT population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Day 197		
n	15	21
LS mean change from baseline	0.16	-0.14
SE	0.312	0.262
95% CI	(-0.477, 0.799)	(-0.677, 0.392)
LS mean difference (tofersen - placebo)		-0.30
SE		0.388
95% CI		(-1.096, 0.489)
p-value		0.4403
Hedge's g standardized mean difference (tofersen - placebo)		-0.25
95% CI		(-0.918, 0.413)
p-value		0.4567

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by gender - ITT population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Day 197		
n	15	37
LS mean change from baseline	0.15	0.43
SE	0.403	0.316
95% CI	(-0.661, 0.962)	(-0.207, 1.065)
LS mean difference (tofersen - placebo)		0.28
SE		0.394
95% CI		(-0.516, 1.072)
p-value		0.4841
Hedge's g standardized mean difference (tofersen - placebo)		0.18
95% CI		(-0.422, 0.779)
p-value		0.5605

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by baseline disease duration since symptom onset - ITT population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Day 197		
n	12	33
LS mean change from baseline	-0.21	0.07
SE	0.398	0.304
95% CI	(-1.013, 0.596)	(-0.547, 0.683)
LS mean difference (tofersen - placebo)		0.28
SE		0.426
95% CI		(-0.585, 1.138)
p-value		0.5196
Hedge's g standardized mean difference (tofersen - placebo)		0.29
95% CI		(-0.371, 0.957)
p-value		0.3869

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by baseline disease duration since symptom onset - ITT population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Day 197		
n	18	25
LS mean change from baseline	0.10	0.18
SE	0.274	0.228
95% CI	(-0.460, 0.650)	(-0.284, 0.639)
LS mean difference (tofersen - placebo)		0.08
SE		0.334
95% CI		(-0.595, 0.759)
p-value		0.8074
Hedge's g standardized mean difference (tofersen - placebo)		-0.14
95% CI		(-0.749, 0.464)
p-value		0.6458

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by baseline plasma NfL level (median) - ITT population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Day 197		
n	18	27
LS mean change from baseline	0.68	0.05
SE	0.249	0.214
95% CI	(0.174, 1.181)	(-0.385, 0.482)
LS mean difference (tofersen - placebo)		-0.63
SE		0.305
95% CI		(-1.245, -0.013)
p-value		0.0457
Hedge's g standardized mean difference (tofersen - placebo)		-0.52
95% CI		(-1.124, 0.089)
p-value		0.0945

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by baseline plasma NfL level (median) - ITT population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Day 197		
n	12	31
LS mean change from baseline	-0.71	0.23
SE	0.440	0.327
95% CI	(-1.600, 0.184)	(-0.436, 0.890)
LS mean difference (tofersen - placebo)		0.94
SE		0.459
95% CI		(0.005, 1.866)
p-value		0.0489
Hedge's g standardized mean difference (tofersen - placebo)		0.62
95% CI		(-0.065, 1.294)
p-value		0.0763

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by riluzole or edaravone use - ITT population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Day 197		
n	18	39
LS mean change from baseline	0.18	0.02
SE	0.277	0.188
95% CI	(-0.378, 0.733)	(-0.356, 0.398)
LS mean difference (tofersen - placebo)		-0.16
SE		0.335
95% CI		(-0.828, 0.515)
p-value		0.6420
Hedge's g standardized mean difference (tofersen - placebo)		-0.17
95% CI		(-0.728, 0.391)
p-value		0.5556

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset and baseline MMSE total score.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-ruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by riluzole or edaravone use - ITT population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Day 197		
n	12	19
LS mean change from baseline	-0.49	-0.17
SE	0.385	0.305
95% CI	(-1.276, 0.302)	(-0.793, 0.460)
LS mean difference (tofersen - placebo)		0.32
SE		0.492
95% CI		(-0.688, 1.329)
p-value		0.5200
Hedge's g standardized mean difference (tofersen - placebo)		0.26
95% CI		(-0.471, 0.980)
p-value		0.4919

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset and baseline MMSE total score.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-ruse.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by prognostic enrichment criteria for rapid disease progression - ITT population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Day 197		
n	18	32
LS mean change from baseline	-0.21	0.04
SE	0.409	0.343
95% CI	(-1.034, 0.614)	(-0.650, 0.732)
LS mean difference (tofersen - placebo)		0.25
SE		0.425
95% CI		(-0.605, 1.108)
p-value		0.5577
Hedge's g standardized mean difference (tofersen - placebo)		0.27
95% CI		(-0.316, 0.844)
p-value		0.3726

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by prognostic enrichment criteria for rapid disease progression - ITT population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Day 197		
n	12	26
LS mean change from baseline	0.46	0.16
SE	0.188	0.131
95% CI	(0.074, 0.841)	(-0.104, 0.431)
LS mean difference (tofersen - placebo)		-0.29
SE		0.219
95% CI		(-0.739, 0.151)
p-value		0.1881
Hedge's g standardized mean difference (tofersen - placebo)		-0.48
95% CI		(-1.172, 0.214)
p-value		0.1752

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by age at first dose - ITT population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Day 197		
n	19	39
LS mean change from baseline	0.10	0.16
SE	0.329	0.239
95% CI	(-0.562, 0.761)	(-0.322, 0.638)
LS mean difference (tofersen - placebo)		0.06
SE		0.357
95% CI		(-0.658, 0.775)
p-value		0.8705
Hedge's g standardized mean difference (tofersen - placebo)		-0.06
95% CI		(-0.605, 0.492)
p-value		0.8395

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: MMSE total score change from baseline at Day 197 ANCOVA analysis (observed data) by age at first dose - ITT population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Day 197		
n	11	19
LS mean change from baseline	0.09	0.10
SE	0.426	0.362
95% CI	(-0.793, 0.965)	(-0.651, 0.845)
LS mean difference (tofersen - placebo)		0.01
SE		0.518
95% CI		(-1.058, 1.079)
p-value		0.9837
Hedge's g standardized mean difference (tofersen - placebo)		0.13
95% CI		(-0.611, 0.876)
p-value		0.7269

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: Based on Protocol Version 7, some subjects had MMSE collected less frequently during post-baseline i.e, Days 85, 169 and 197 so these subjects are not summarized at other post-baseline visits.
NOTE 4: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-sgrp.sas:t-mmse-chg-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 27JUL2023

233AS101 Part C: Number of subjects with at least one adverse event: treatment by subgroup interaction - safety population

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Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.4011	0.4468	0.3952
Baseline disease duration since symptom onset by median	0.5030	0.3781	0.4938
Baseline NfL plasma level by median	0.4499	0.3473	0.4414
Riluzole or edaravone use	0.4754	0.5202	0.4735
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.2824	0.2312	0.2717
Age at first dose (<55, >=55)	0.0876	0.0874	0.0656

Source: biib067/valueaccess/amnog/t-ae-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JAN2023

233AS101 Part C: Number of subjects with at least one adverse event by gender - safety population

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Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with any event	17 (100)	28 (96.6)
RR - Relative Risk (tofersen/placebo)		0.98
SE of log (RR)		0.058
95% CI		(0.872, 1.094)
p-value		0.6892
OR - Odds Ratio (tofersen/placebo)		0.54
SE of log (OR)		1.661
95% CI		(0.021, 14.077)
p-value		0.7130
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.02
SE of ARR		0.056
95% CI		(-0.131, 0.087)
p-value		0.6890

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by gender - safety population

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Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with any event	17 (89.5)	41 (95.3)
RR - Relative Risk (tofersen/placebo)		1.07
SE of log (RR)		0.086
95% CI		(0.901, 1.260)
p-value		0.4575
OR - Odds Ratio (tofersen/placebo)		2.41
SE of log (OR)		1.041
95% CI		(0.314, 18.546)
p-value		0.3976
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.077
95% CI		(-0.093, 0.210)
p-value		0.4477

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by baseline disease duration since symptom onset (median) - safety population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with any event	14 (93.3)	35 (92.1)
RR - Relative Risk (tofersen/placebo)		0.99
SE of log (RR)		0.084
95% CI		(0.837, 1.163)
p-value		0.8744
OR - Odds Ratio (tofersen/placebo)		0.83
SE of log (OR)		1.197
95% CI		(0.080, 8.707)
p-value		0.8790
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.078
95% CI		(-0.165, 0.140)
p-value		0.8747

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by baseline disease duration since symptom onset (median) - safety population

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>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with any event	20 (95.2)	34 (100)
RR - Relative Risk (tofersen/placebo)		1.06
SE of log (RR)		0.061
95% CI		(0.938, 1.193)
p-value		0.3579
OR - Odds Ratio (tofersen/placebo)		5.05
SE of log (OR)		1.657
95% CI		(0.196, 129.812)
p-value		0.3284
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.057
95% CI		(-0.059, 0.166)
p-value		0.3474

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by baseline plasma NfL level (median) - safety population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with any event	19 (95.0)	34 (100)
RR - Relative Risk (tofersen/placebo)		1.06
SE of log (RR)		0.064
95% CI		(0.937, 1.203)
p-value		0.3496
OR - Odds Ratio (tofersen/placebo)		5.31
SE of log (OR)		1.657
95% CI		(0.206, 136.671)
p-value		0.3139
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.060
95% CI		(-0.060, 0.174)
p-value		0.3383

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by baseline plasma NfL level (median) - safety population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with any event	15 (93.8)	35 (92.1)
RR - Relative Risk (tofersen/placebo)		0.98
SE of log (RR)		0.080
95% CI		(0.840, 1.150)
p-value		0.8252
OR - Odds Ratio (tofersen/placebo)		0.78
SE of log (OR)		1.195
95% CI		(0.075, 8.095)
p-value		0.8335
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.02
SE of ARR		0.075
95% CI		(-0.163, 0.130)
p-value		0.8257

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by riluzole or edaravone use - safety population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with any event	20 (90.9)	43 (95.6)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.075
95% CI		(0.908, 1.217)
p-value		0.5045
OR - Odds Ratio (tofersen/placebo)		2.15
SE of log (OR)		1.036
95% CI		(0.282, 16.378)
p-value		0.4600
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.069
95% CI		(-0.088, 0.181)
p-value		0.4979

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by riluzole or edaravone use - safety population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with any event	14 (100)	26 (96.3)
RR - Relative Risk (tofersen/placebo)		0.98
SE of log (RR)		0.066
95% CI		(0.861, 1.114)
p-value		0.7475
OR - Odds Ratio (tofersen/placebo)		0.61
SE of log (OR)		1.665
95% CI		(0.023, 15.933)
p-value		0.7660
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.02
SE of ARR		0.063
95% CI		(-0.144, 0.103)
p-value		0.7477

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by prognostic enrichment criteria for rapid disease progression - safety population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with any event	20 (95.2)	36 (92.3)
RR - Relative Risk (tofersen/placebo)		0.97
SE of log (RR)		0.067
95% CI		(0.850, 1.106)
p-value		0.6420
OR - Odds Ratio (tofersen/placebo)		0.60
SE of log (OR)		1.188
95% CI		(0.058, 6.156)
p-value		0.6672
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.063
95% CI		(-0.153, 0.094)
p-value		0.6423

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by prognostic enrichment criteria for rapid disease progression - safety population

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Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with any event	14 (93.3)	33 (100)
RR - Relative Risk (tofersen/placebo)		1.09
SE of log (RR)		0.083
95% CI		(0.924, 1.280)
p-value		0.3142
OR - Odds Ratio (tofersen/placebo)		6.93
SE of log (OR)		1.663
95% CI		(0.266, 180.436)
p-value		0.2443
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.076
95% CI		(-0.069, 0.227)
p-value		0.2966

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by age at first dose - safety population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with any event	23 (100)	43 (93.5)
RR - Relative Risk (tofersen/placebo)		0.95
SE of log (RR)		0.051
95% CI		(0.855, 1.045)
p-value		0.2691
OR - Odds Ratio (tofersen/placebo)		0.26
SE of log (OR)		1.533
95% CI		(0.013, 5.340)
p-value		0.3857
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.05
SE of ARR		0.048
95% CI		(-0.148, 0.041)
p-value		0.2651

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by age at first dose - safety population

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>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with any event	11 (84.6)	26 (100)
RR - Relative Risk (tofersen/placebo)		1.19
SE of log (RR)		0.127
95% CI		(0.931, 1.534)
p-value		0.1623
OR - Odds Ratio (tofersen/placebo)		11.52
SE of log (OR)		1.589
95% CI		(0.512, 259.428)
p-value		0.1240
ARR - Absolute Risk Reduction (tofersen/placebo)		0.16
SE of ARR		0.106
95% CI		(-0.047, 0.367)
p-value		0.1296

Source: biib067/valueaccess/amnog/t-ae-event-sgrp.sas:t-ae-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class: treatment by subgroup interaction - safety population

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Infections and infestations

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.3660	0.3557	0.3560
Baseline disease duration since symptom onset by median	0.1228	0.2061	0.4853
Baseline NfL plasma level by median	0.0677	0.0963	0.1794
Riluzole or edaravone use	0.7284	0.5368	0.3764
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.2846	0.4931	0.8716
Age at first dose (<55, >=55)	0.6218	0.4621	0.2609

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.

NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).

Source: biib067/valueaccess/amnog/t-ae-soc-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 23MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term: treatment by subgroup interaction - safety population

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Injury, poisoning and procedural complications/Fall

Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.5530	0.4382	0.3301
Baseline disease duration since symptom onset by median	0.6243	0.7453	0.8879
Baseline NfL plasma level by median	0.8171	0.9791	0.8468
Riluzole or edaravone use	0.5510	0.6209	0.7001
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.6334	0.8513	0.8067
Age at first dose (<55, >=55)	0.8381	0.7271	0.5979

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.

NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).

Source: biib067/valueaccess/amnog/t-ae-pt-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 28MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by gender - safety population

Infections and infestations, Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with any event	6 (35.3)	7 (24.1)
RR - Relative Risk (tofersen/placebo)		0.68
SE of log (RR)		0.465
95% CI		(0.275, 1.701)
p-value		0.4139
OR - Odds Ratio (tofersen/placebo)		0.58
SE of log (OR)		0.668
95% CI		(0.158, 2.159)
p-value		0.4196
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.141
95% CI		(-0.387, 0.164)
p-value		0.4273

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by gender - safety population

Infections and infestations, Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with any event	9 (47.4)	8 (18.6)
RR - Relative Risk (tofersen/placebo)		0.39
SE of log (RR)		0.400
95% CI		(0.179, 0.861)
p-value		0.0196
OR - Odds Ratio (tofersen/placebo)		0.25
SE of log (OR)		0.604
95% CI		(0.078, 0.829)
p-value		0.0232
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.29
SE of ARR		0.129
95% CI		(-0.540, -0.035)
p-value		0.0258

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by baseline disease duration since symptom onset (median) - safety population

Infections and infestations, < Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with any event	5 (33.3)	3 (7.9)
RR - Relative Risk (tofersen/placebo)		0.24
SE of log (RR)		0.664
95% CI		(0.065, 0.870)
p-value		0.0300
OR - Odds Ratio (tofersen/placebo)		0.17
SE of log (OR)		0.814
95% CI		(0.035, 0.845)
p-value		0.0302
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.25
SE of ARR		0.129
95% CI		(-0.508, -0.001)
p-value		0.0492

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by baseline disease duration since symptom onset (median) - safety population

Infections and infestations, >= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with any event	10 (47.6)	12 (35.3)
RR - Relative Risk (tofersen/placebo)		0.74
SE of log (RR)		0.326
95% CI		(0.391, 1.404)
p-value		0.3583
OR - Odds Ratio (tofersen/placebo)		0.60
SE of log (OR)		0.565
95% CI		(0.198, 1.817)
p-value		0.3663
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.12
SE of ARR		0.136
95% CI		(-0.391, 0.144)
p-value		0.3661

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by baseline plasma NfL level (median) - safety population

Infections and infestations, < Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with any event	8 (40.0)	11 (32.4)
RR - Relative Risk (tofersen/placebo)		0.81
SE of log (RR)		0.369
95% CI		(0.392, 1.669)
p-value		0.5658
OR - Odds Ratio (tofersen/placebo)		0.72
SE of log (OR)		0.585
95% CI		(0.228, 2.260)
p-value		0.5705
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.136
95% CI		(-0.343, 0.190)
p-value		0.5733

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by baseline plasma NfL level (median) - safety population

Infections and infestations, >= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with any event	7 (43.8)	4 (10.5)
RR - Relative Risk (tofersen/placebo)		0.24
SE of log (RR)		0.551
95% CI		(0.082, 0.709)
p-value		0.0098
OR - Odds Ratio (tofersen/placebo)		0.15
SE of log (OR)		0.730
95% CI		(0.036, 0.633)
p-value		0.0097
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.33
SE of ARR		0.134
95% CI		(-0.594, -0.070)
p-value		0.0129

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by riluzole or edaravone use - safety population

Infections and infestations, Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with any event	7 (31.8)	8 (17.8)
RR - Relative Risk (tofersen/placebo)		0.56
SE of log (RR)		0.447
95% CI		(0.232, 1.343)
p-value		0.1933
OR - Odds Ratio (tofersen/placebo)		0.46
SE of log (OR)		0.601
95% CI		(0.143, 1.506)
p-value		0.2007
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.14
SE of ARR		0.114
95% CI		(-0.365, 0.084)
p-value		0.2201

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by riluzole or edaravone use - safety population

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Infections and infestations, Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with any event	8 (57.1)	7 (25.9)
RR - Relative Risk (tofersen/placebo)		0.45
SE of log (RR)		0.399
95% CI		(0.207, 0.992)
p-value		0.0478
OR - Odds Ratio (tofersen/placebo)		0.26
SE of log (OR)		0.696
95% CI		(0.067, 1.027)
p-value		0.0547
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.31
SE of ARR		0.157
95% CI		(-0.620, -0.005)
p-value		0.0466

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by prognostic enrichment criteria for rapid disease progression - safety population

Infections and infestations, mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with any event	7 (33.3)	4 (10.3)
RR - Relative Risk (tofersen/placebo)		0.31
SE of log (RR)		0.565
95% CI		(0.102, 0.932)
p-value		0.0371
OR - Odds Ratio (tofersen/placebo)		0.23
SE of log (OR)		0.702
95% CI		(0.058, 0.905)
p-value		0.0355
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.23
SE of ARR		0.114
95% CI		(-0.454, -0.008)
p-value		0.0425

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by prognostic enrichment criteria for rapid disease progression - safety population

Infections and infestations, Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with any event	8 (53.3)	11 (33.3)
RR - Relative Risk (tofersen/placebo)		0.63
SE of log (RR)		0.345
95% CI		(0.318, 1.229)
p-value		0.1729
OR - Odds Ratio (tofersen/placebo)		0.44
SE of log (OR)		0.636
95% CI		(0.126, 1.521)
p-value		0.1935
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.20
SE of ARR		0.153
95% CI		(-0.499, 0.099)
p-value		0.1904

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by age at first dose - safety population

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Infections and infestations, < 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with any event	12 (52.2)	11 (23.9)
RR - Relative Risk (tofersen/placebo)		0.46
SE of log (RR)		0.330
95% CI		(0.240, 0.875)
p-value		0.0181
OR - Odds Ratio (tofersen/placebo)		0.29
SE of log (OR)		0.542
95% CI		(0.100, 0.833)
p-value		0.0217
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.28
SE of ARR		0.122
95% CI		(-0.521, -0.044)
p-value		0.0202

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by system organ class by age at first dose - safety population

Infections and infestations, >= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with any event	3 (23.1)	4 (15.4)
RR - Relative Risk (tofersen/placebo)		0.67
SE of log (RR)		0.684
95% CI		(0.174, 2.548)
p-value		0.5534
OR - Odds Ratio (tofersen/placebo)		0.61
SE of log (OR)		0.854
95% CI		(0.114, 3.230)
p-value		0.5575
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.137
95% CI		(-0.345, 0.191)
p-value		0.5734

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-sgrp.sas:t-ae-soc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by gender - safety population

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Injury, poisoning and procedural complications/Fall, Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with any event	5 (29.4)	6 (20.7)
RR - Relative Risk (tofersen/placebo)		0.70
SE of log (RR)		0.523
95% CI		(0.252, 1.960)
p-value		0.5011
OR - Odds Ratio (tofersen/placebo)		0.63
SE of log (OR)		0.702
95% CI		(0.158, 2.481)
p-value		0.5050
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.09
SE of ARR		0.134
95% CI		(-0.349, 0.175)
p-value		0.5141

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by gender - safety population

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Injury, poisoning and procedural complications/Fall, Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with any event	10 (52.6)	11 (25.6)
RR - Relative Risk (tofersen/placebo)		0.49
SE of log (RR)		0.339
95% CI		(0.250, 0.945)
p-value		0.0334
OR - Odds Ratio (tofersen/placebo)		0.31
SE of log (OR)		0.577
95% CI		(0.100, 0.959)
p-value		0.0421
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.27
SE of ARR		0.132
95% CI		(-0.530, -0.011)
p-value		0.0412

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by baseline disease duration since symptom onset (median) - safety population

Injury, poisoning and procedural complications/Fall, < Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with any event	7 (46.7)	11 (28.9)
RR - Relative Risk (tofersen/placebo)		0.62
SE of log (RR)		0.375
95% CI		(0.297, 1.294)
p-value		0.2031
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.629
95% CI		(0.136, 1.598)
p-value		0.2244
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.18
SE of ARR		0.148
95% CI		(-0.468, 0.114)
p-value		0.2323

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by baseline disease duration since symptom onset (median) - safety population

Injury, poisoning and procedural complications/Fall, >= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with any event	8 (38.1)	6 (17.6)
RR - Relative Risk (tofersen/placebo)		0.46
SE of log (RR)		0.463
95% CI		(0.187, 1.149)
p-value		0.0967
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.636
95% CI		(0.100, 1.211)
p-value		0.0971
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.20
SE of ARR		0.125
95% CI		(-0.449, 0.040)
p-value		0.1005

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by baseline plasma NfL level (median) - safety population

Injury, poisoning and procedural complications/Fall, < Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with any event	7 (35.0)	6 (17.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.480
95% CI		(0.197, 1.291)
p-value		0.1534
OR - Odds Ratio (tofersen/placebo)		0.40
SE of log (OR)		0.650
95% CI		(0.111, 1.422)
p-value		0.1562
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.17
SE of ARR		0.125
95% CI		(-0.419, 0.072)
p-value		0.1654

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by baseline plasma NfL level (median) - safety population

Injury, poisoning and procedural complications/Fall, >= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with any event	8 (50.0)	11 (28.9)
RR - Relative Risk (tofersen/placebo)		0.58
SE of log (RR)		0.357
95% CI		(0.288, 1.164)
p-value		0.1253
OR - Odds Ratio (tofersen/placebo)		0.41
SE of log (OR)		0.615
95% CI		(0.122, 1.359)
p-value		0.1441
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.21
SE of ARR		0.145
95% CI		(-0.495, 0.074)
p-value		0.1466

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by riluzole or edaravone use - safety population

Page: 1 of 2

Injury, poisoning and procedural complications/Fall, Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with any event	9 (40.9)	9 (20.0)
RR - Relative Risk (tofersen/placebo)		0.49
SE of log (RR)		0.393
95% CI		(0.226, 1.056)
p-value		0.0687
OR - Odds Ratio (tofersen/placebo)		0.36
SE of log (OR)		0.572
95% CI		(0.118, 1.107)
p-value		0.0748
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.21
SE of ARR		0.121
95% CI		(-0.445, 0.027)
p-value		0.0830

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by riluzole or edaravone use - safety population

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Injury, poisoning and procedural complications/Fall, Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with any event	6 (42.9)	8 (29.6)
RR - Relative Risk (tofersen/placebo)		0.69
SE of log (RR)		0.428
95% CI		(0.299, 1.600)
p-value		0.3885
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.685
95% CI		(0.147, 2.150)
p-value		0.3994
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.159
95% CI		(-0.444, 0.179)
p-value		0.4048

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by prognostic enrichment criteria for rapid disease progression - safety population

Injury, poisoning and procedural complications/Fall, mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with any event	11 (52.4)	13 (33.3)
RR - Relative Risk (tofersen/placebo)		0.64
SE of log (RR)		0.308
95% CI		(0.348, 1.163)
p-value		0.1416
OR - Odds Ratio (tofersen/placebo)		0.45
SE of log (OR)		0.553
95% CI		(0.154, 1.345)
p-value		0.1543
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.19
SE of ARR		0.133
95% CI		(-0.450, 0.069)
p-value		0.1508

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by prognostic enrichment criteria for rapid disease progression - safety population

Injury, poisoning and procedural complications/Fall, Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with any event	4 (26.7)	4 (12.1)
RR - Relative Risk (tofersen/placebo)		0.45
SE of log (RR)		0.635
95% CI		(0.131, 1.577)
p-value		0.2142
OR - Odds Ratio (tofersen/placebo)		0.38
SE of log (OR)		0.791
95% CI		(0.081, 1.787)
p-value		0.2203
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.15
SE of ARR		0.128
95% CI		(-0.395, 0.105)
p-value		0.2541

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by age at first dose - safety population

Injury, poisoning and procedural complications/Fall, < 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with any event	11 (47.8)	12 (26.1)
RR - Relative Risk (tofersen/placebo)		0.55
SE of log (RR)		0.330
95% CI		(0.286, 1.042)
p-value		0.0664
OR - Odds Ratio (tofersen/placebo)		0.39
SE of log (OR)		0.536
95% CI		(0.135, 1.100)
p-value		0.0748
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.22
SE of ARR		0.123
95% CI		(-0.458, 0.023)
p-value		0.0763

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event by preferred term by age at first dose - safety population

Injury, poisoning and procedural complications/Fall, >= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with any event	4 (30.8)	5 (19.2)
RR - Relative Risk (tofersen/placebo)		0.63
SE of log (RR)		0.578
95% CI		(0.201, 1.942)
p-value		0.4165
OR - Odds Ratio (tofersen/placebo)		0.54
SE of log (OR)		0.780
95% CI		(0.116, 2.472)
p-value		0.4237
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.12
SE of ARR		0.150
95% CI		(-0.408, 0.178)
p-value		0.4403

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-sgrp.sas:t-ae-pt-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event: treatment by subgroup interaction - safety population

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Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.5884	0.5839	0.5690
Baseline disease duration since symptom onset by median	0.9667	0.9864	0.9235
Baseline NfL plasma level by median	0.6747	0.6942	0.8644
Riluzole or edaravone use	0.9954	0.9971	0.9952
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.7058	0.6670	0.4718
Age at first dose (<55, >=55)	0.9480	0.9528	0.9742

Source: biib067/valueaccess/amnog/t-sae-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JAN2023

233AS101 Part C: Number of subjects with at least one serious adverse event by gender - safety population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with any serious event	2 (11.8)	6 (20.7)
RR - Relative Risk (tofersen/placebo)		1.76
SE of log (RR)		0.757
95% CI		(0.399, 7.757)
p-value		0.4559
OR - Odds Ratio (tofersen/placebo)		1.96
SE of log (OR)		0.881
95% CI		(0.348, 11.008)
p-value		0.4464
ARR - Absolute Risk Reduction (tofersen/placebo)		0.09
SE of ARR		0.108
95% CI		(-0.123, 0.302)
p-value		0.4106

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by gender - safety population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with any serious event	3 (15.8)	7 (16.3)
RR - Relative Risk (tofersen/placebo)		1.03
SE of log (RR)		0.633
95% CI		(0.298, 3.563)
p-value		0.9615
OR - Odds Ratio (tofersen/placebo)		1.04
SE of log (OR)		0.753
95% CI		(0.237, 4.534)
p-value		0.9615
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.101
95% CI		(-0.193, 0.203)
p-value		0.9613

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by baseline disease duration since symptom onset (median) - safety population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with any serious event	3 (20.0)	9 (23.7)
RR - Relative Risk (tofersen/placebo)		1.18
SE of log (RR)		0.593
95% CI		(0.371, 3.785)
p-value		0.7755
OR - Odds Ratio (tofersen/placebo)		1.24
SE of log (OR)		0.750
95% CI		(0.286, 5.397)
p-value		0.7731
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.124
95% CI		(-0.207, 0.280)
p-value		0.7667

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by baseline disease duration since symptom onset (median) - safety population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with any serious event	2 (9.5)	4 (11.8)
RR - Relative Risk (tofersen/placebo)		1.24
SE of log (RR)		0.820
95% CI		(0.247, 6.167)
p-value		0.7967
OR - Odds Ratio (tofersen/placebo)		1.27
SE of log (OR)		0.914
95% CI		(0.211, 7.602)
p-value		0.7960
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.085
95% CI		(-0.143, 0.188)
p-value		0.7911

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by baseline plasma NfL level (median) - safety population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with any serious event	1 (5.0)	3 (8.8)
RR - Relative Risk (tofersen/placebo)		1.76
SE of log (RR)		1.120
95% CI		(0.197, 15.843)
p-value		0.6120
OR - Odds Ratio (tofersen/placebo)		1.84
SE of log (OR)		1.191
95% CI		(0.178, 18.976)
p-value		0.6090
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.069
95% CI		(-0.097, 0.173)
p-value		0.5787

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by baseline plasma NfL level (median) - safety population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with any serious event	4 (25.0)	10 (26.3)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.511
95% CI		(0.387, 2.866)
p-value		0.9201
OR - Odds Ratio (tofersen/placebo)		1.07
SE of log (OR)		0.685
95% CI		(0.280, 4.101)
p-value		0.9198
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.130
95% CI		(-0.241, 0.267)
p-value		0.9192

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by riluzole or edaravone use - safety population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with any serious event	3 (13.6)	8 (17.8)
RR - Relative Risk (tofersen/placebo)		1.30
SE of log (RR)		0.625
95% CI		(0.383, 4.438)
p-value		0.6713
OR - Odds Ratio (tofersen/placebo)		1.37
SE of log (OR)		0.733
95% CI		(0.325, 5.766)
p-value		0.6682
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.093
95% CI		(-0.140, 0.223)
p-value		0.6552

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by riluzole or edaravone use - safety population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with any serious event	2 (14.3)	5 (18.5)
RR - Relative Risk (tofersen/placebo)		1.30
SE of log (RR)		0.769
95% CI		(0.287, 5.853)
p-value		0.7358
OR - Odds Ratio (tofersen/placebo)		1.36
SE of log (OR)		0.910
95% CI		(0.229, 8.121)
p-value		0.7333
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.120
95% CI		(-0.192, 0.277)
p-value		0.7237

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by prognostic enrichment criteria for rapid disease progression - safety population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with any serious event	4 (19.0)	11 (28.2)
RR - Relative Risk (tofersen/placebo)		1.48
SE of log (RR)		0.517
95% CI		(0.537, 4.082)
p-value		0.4480
OR - Odds Ratio (tofersen/placebo)		1.67
SE of log (OR)		0.660
95% CI		(0.458, 6.086)
p-value		0.4373
ARR - Absolute Risk Reduction (tofersen/placebo)		0.09
SE of ARR		0.112
95% CI		(-0.128, 0.311)
p-value		0.4134

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by prognostic enrichment criteria for rapid disease progression - safety population

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Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with any serious event	1 (6.7)	2 (6.1)
RR - Relative Risk (tofersen/placebo)		0.91
SE of log (RR)		1.184
95% CI		(0.089, 9.265)
p-value		0.9359
OR - Odds Ratio (tofersen/placebo)		0.90
SE of log (OR)		1.266
95% CI		(0.075, 10.808)
p-value		0.9359
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.077
95% CI		(-0.156, 0.144)
p-value		0.9370

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by age at first dose - safety population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with any serious event	3 (13.0)	8 (17.4)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.627
95% CI		(0.390, 4.557)
p-value		0.6464
OR - Odds Ratio (tofersen/placebo)		1.40
SE of log (OR)		0.731
95% CI		(0.335, 5.883)
p-value		0.6429
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.090
95% CI		(-0.132, 0.219)
p-value		0.6281

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by age at first dose - safety population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with any serious event	2 (15.4)	5 (19.2)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.765
95% CI		(0.279, 5.594)
p-value		0.7704
OR - Odds Ratio (tofersen/placebo)		1.31
SE of log (OR)		0.916
95% CI		(0.218, 7.881)
p-value		0.7684
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.126
95% CI		(-0.209, 0.286)
p-value		0.7610

Source: biib067/valueaccess/amnog/t-sae-event-sgrp.sas:t-sae-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one serious adverse event by system organ class: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

233AS101 Part C: Number of subjects with at least one serious adverse event by preferred term: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3: treatment by subgroup interaction - safety population

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Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.7933	0.7770	0.6939
Baseline disease duration since symptom onset by median	0.6781	0.6783	0.6855
Baseline NfL plasma level by median	0.3445	0.3465	0.5291
Riluzole or edaravone use	0.5027	0.4977	0.4881
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.8937	0.8579	0.6257
Age at first dose (<55, >=55)	0.5332	0.5259	0.4988

Source: biib067/valueaccess/amnog/t-ae-ctc-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JAN2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by gender - safety population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with any grade >= 3 event	2 (11.8)	6 (20.7)
RR - Relative Risk (tofersen/placebo)		1.76
SE of log (RR)		0.757
95% CI		(0.399, 7.757)
p-value		0.4559
OR - Odds Ratio (tofersen/placebo)		1.96
SE of log (OR)		0.881
95% CI		(0.348, 11.008)
p-value		0.4464
ARR - Absolute Risk Reduction (tofersen/placebo)		0.09
SE of ARR		0.108
95% CI		(-0.123, 0.302)
p-value		0.4106

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by gender - safety population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with any grade >= 3 event	2 (10.5)	6 (14.0)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.769
95% CI		(0.294, 5.979)
p-value		0.7138
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.867
95% CI		(0.252, 7.547)
p-value		0.7114
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.088
95% CI		(-0.138, 0.207)
p-value		0.6970

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by baseline disease duration since symptom onset (median) - safety population

< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with any grade >= 3 event	2 (13.3)	6 (15.8)
RR - Relative Risk (tofersen/placebo)		1.18
SE of log (RR)		0.757
95% CI		(0.268, 5.226)
p-value		0.8234
OR - Odds Ratio (tofersen/placebo)		1.22
SE of log (OR)		0.880
95% CI		(0.217, 6.842)
p-value		0.8222
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.106
95% CI		(-0.183, 0.232)
p-value		0.8165

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by baseline disease duration since symptom onset (median) - safety population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with any grade >= 3 event	2 (9.5)	6 (17.6)
RR - Relative Risk (tofersen/placebo)		1.85
SE of log (RR)		0.768
95% CI		(0.411, 8.346)
p-value		0.4218
OR - Odds Ratio (tofersen/placebo)		2.04
SE of log (OR)		0.869
95% CI		(0.371, 11.177)
p-value		0.4133
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.092
95% CI		(-0.098, 0.261)
p-value		0.3748

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by baseline plasma NfL level (median) - safety population

< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with any grade >= 3 event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.20
SE of log (RR)		1.486
95% CI		(0.228, 77.360)
p-value		0.3343
OR - Odds Ratio (tofersen/placebo)		4.56
SE of log (OR)		1.538
95% CI		(0.223, 92.877)
p-value		0.3243
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.061
95% CI		(-0.043, 0.195)
p-value		0.2090

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by baseline plasma NfL level (median) - safety population

>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with any grade >= 3 event	4 (25.0)	9 (23.7)
RR - Relative Risk (tofersen/placebo)		0.95
SE of log (RR)		0.522
95% CI		(0.341, 2.634)
p-value		0.9175
OR - Odds Ratio (tofersen/placebo)		0.93
SE of log (OR)		0.692
95% CI		(0.240, 3.614)
p-value		0.9178
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.128
95% CI		(-0.265, 0.238)
p-value		0.9184

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by riluzole or edaravone use - safety population

Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with any grade >= 3 event	3 (13.6)	7 (15.6)
RR - Relative Risk (tofersen/placebo)		1.14
SE of log (RR)		0.639
95% CI		(0.326, 3.992)
p-value		0.8368
OR - Odds Ratio (tofersen/placebo)		1.17
SE of log (OR)		0.745
95% CI		(0.271, 5.025)
p-value		0.8361
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.091
95% CI		(-0.159, 0.197)
p-value		0.8329

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by riluzole or edaravone use - safety population

Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with any grade >= 3 event	1 (7.1)	5 (18.5)
RR - Relative Risk (tofersen/placebo)		2.59
SE of log (RR)		1.045
95% CI		(0.335, 20.093)
p-value		0.3619
OR - Odds Ratio (tofersen/placebo)		2.95
SE of log (OR)		1.150
95% CI		(0.310, 28.140)
p-value		0.3462
ARR - Absolute Risk Reduction (tofersen/placebo)		0.11
SE of ARR		0.102
95% CI		(-0.085, 0.313)
p-value		0.2629

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by prognostic enrichment criteria for rapid disease progression - safety population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with any grade >= 3 event	3 (14.3)	9 (23.1)
RR - Relative Risk (tofersen/placebo)		1.62
SE of log (RR)		0.609
95% CI		(0.489, 5.332)
p-value		0.4312
OR - Odds Ratio (tofersen/placebo)		1.80
SE of log (OR)		0.730
95% CI		(0.430, 7.532)
p-value		0.4209
ARR - Absolute Risk Reduction (tofersen/placebo)		0.09
SE of ARR		0.102
95% CI		(-0.112, 0.288)
p-value		0.3883

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by prognostic enrichment criteria for rapid disease progression - safety population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with any grade >= 3 event	1 (6.7)	3 (9.1)
RR - Relative Risk (tofersen/placebo)		1.36
SE of log (RR)		1.112
95% CI		(0.154, 12.055)
p-value		0.7803
OR - Odds Ratio (tofersen/placebo)		1.40
SE of log (OR)		1.199
95% CI		(0.133, 14.686)
p-value		0.7790
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.082
95% CI		(-0.136, 0.184)
p-value		0.7663

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by age at first dose - safety population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with any grade >= 3 event	3 (13.0)	7 (15.2)
RR - Relative Risk (tofersen/placebo)		1.17
SE of log (RR)		0.641
95% CI		(0.332, 4.099)
p-value		0.8100
OR - Odds Ratio (tofersen/placebo)		1.20
SE of log (OR)		0.743
95% CI		(0.279, 5.132)
p-value		0.8091
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.088
95% CI		(-0.151, 0.194)
p-value		0.8048

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event with CTCAE grade >= 3 by age at first dose - safety population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with any grade >= 3 event	1 (7.7)	5 (19.2)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		1.041
95% CI		(0.325, 19.250)
p-value		0.3790
OR - Odds Ratio (tofersen/placebo)		2.86
SE of log (OR)		1.154
95% CI		(0.298, 27.412)
p-value		0.3628
ARR - Absolute Risk Reduction (tofersen/placebo)		0.12
SE of ARR		0.107
95% CI		(-0.094, 0.325)
p-value		0.2806

Source: biib067/valueaccess/amnog/t-ae-ctc-event-sgrp.sas:t-ae-ctc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event CTCAE grade >= 3 by system organ class: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

233AS101 Part C: Number of subjects with at least one serious adverse event by preferred term: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation: treatment by subgroup interaction - safety population

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Subgroup	p-Value Based on RR for Treatment by Subgroup Interaction	p-Value Based on OR for Treatment by Subgroup Interaction	p-Value Based on ARR for Treatment by Subgroup Interaction
Gender (female, male)	0.6073	0.5925	0.3368
Baseline disease duration since symptom onset by median	0.8476	0.8382	0.6252
Baseline NfL plasma level by median	0.8095	0.8003	0.5957
Riluzole or edaravone use	0.9744	0.9661	0.7817
Prognostic enrichment criteria for rapid disease progression (mITT, non-mITT)	0.6467	0.6400	0.5076
Age at first dose (<55, >=55)	0.7036	0.7017	0.6802

Source: biib067/valueaccess/amnog/t-ae-disc-event-int.sas **Data Cutoff:** 16JUL2021 **Run Date:** 27JAN2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by gender - safety population

Female

	placebo (N=17)	tofersen 100 mg (N=29)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.20
SE of log (RR)		1.482
95% CI		(0.230, 76.714)
p-value		0.3329
OR - Odds Ratio (tofersen/placebo)		4.62
SE of log (OR)		1.543
95% CI		(0.225, 95.109)
p-value		0.3211
ARR - Absolute Risk Reduction (tofersen/placebo)		0.09
SE of ARR		0.070
95% CI		(-0.049, 0.227)
p-value		0.2058

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by gender - safety population

Male

	placebo (N=19)	tofersen 100 mg (N=43)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.36
SE of log (RR)		1.611
95% CI		(0.058, 32.035)
p-value		0.8473
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		1.656
95% CI		(0.054, 35.329)
p-value		0.8470
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.044
95% CI		(-0.078, 0.096)
p-value		0.8376

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-gen.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by baseline disease duration since symptom onset (median) - safety population

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< Median (11.79 months)

	placebo (N=15)	tofersen 100 mg (N=38)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		2.87
SE of log (RR)		1.482
95% CI		(0.157, 52.480)
p-value		0.4767
OR - Odds Ratio (tofersen/placebo)		3.06
SE of log (OR)		1.542
95% CI		(0.149, 62.796)
p-value		0.4688
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.063
95% CI		(-0.065, 0.182)
p-value		0.3542

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by baseline disease duration since symptom onset (median) - safety population

>= Median (11.79 months)

	placebo (N=21)	tofersen 100 mg (N=34)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		1.89
SE of log (RR)		1.610
95% CI		(0.080, 44.264)
p-value		0.6936
OR - Odds Ratio (tofersen/placebo)		1.93
SE of log (OR)		1.656
95% CI		(0.075, 49.463)
p-value		0.6924
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.047
95% CI		(-0.071, 0.112)
p-value		0.6665

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-ddur.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by baseline plasma NfL level (median) - safety population

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< Median (75.60 pg/mL)

	placebo (N=20)	tofersen 100 mg (N=34)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.80
SE of log (RR)		1.609
95% CI		(0.077, 42.197)
p-value		0.7150
OR - Odds Ratio (tofersen/placebo)		1.84
SE of log (OR)		1.657
95% CI		(0.071, 47.226)
p-value		0.7139
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.048
95% CI		(-0.075, 0.113)
p-value		0.6899

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by baseline plasma NfL level (median) - safety population

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>= Median (75.60 pg/mL)

	placebo (N=16)	tofersen 100 mg (N=38)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		3.05
SE of log (RR)		1.484
95% CI		(0.167, 55.895)
p-value		0.4521
OR - Odds Ratio (tofersen/placebo)		3.25
SE of log (OR)		1.541
95% CI		(0.159, 66.681)
p-value		0.4439
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.061
95% CI		(-0.060, 0.181)
p-value		0.3261

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-med.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by riluzole or edaravone use - safety population

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Edaravone or Riluzole Use

	placebo (N=22)	tofersen 100 mg (N=45)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		1.528
95% CI		(0.125, 49.955)
p-value		0.5487
OR - Odds Ratio (tofersen/placebo)		2.59
SE of log (OR)		1.571
95% CI		(0.119, 56.200)
p-value		0.5452
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.045
95% CI		(-0.056, 0.121)
p-value		0.4705

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by riluzole or edaravone use - safety population

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Neither

	placebo (N=14)	tofersen 100 mg (N=27)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		2.68
SE of log (RR)		1.516
95% CI		(0.137, 52.257)
p-value		0.5157
OR - Odds Ratio (tofersen/placebo)		2.84
SE of log (OR)		1.584
95% CI		(0.128, 63.367)
p-value		0.5094
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.071
95% CI		(-0.083, 0.195)
p-value		0.4312

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-ried.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by prognostic enrichment criteria for rapid disease progression - safety population

mITT population

	placebo (N=21)	tofersen 100 mg (N=39)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		3.85
SE of log (RR)		1.488
95% CI		(0.208, 71.182)
p-value		0.3651
OR - Odds Ratio (tofersen/placebo)		4.12
SE of log (OR)		1.536
95% CI		(0.203, 83.710)
p-value		0.3564
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.055
95% CI		(-0.043, 0.172)
p-value		0.2374

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by prognostic enrichment criteria for rapid disease progression - safety population

Non mITT population

	placebo (N=15)	tofersen 100 mg (N=33)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.41
SE of log (RR)		1.605
95% CI		(0.061, 32.780)
p-value		0.8298
OR - Odds Ratio (tofersen/placebo)		1.43
SE of log (OR)		1.662
95% CI		(0.055, 37.170)
p-value		0.8293
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.056
95% CI		(-0.097, 0.123)
p-value		0.8182

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-dprog.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by age at first dose - safety population

< 55 years

	placebo (N=23)	tofersen 100 mg (N=46)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		3.57
SE of log (RR)		1.491
95% CI		(0.192, 66.415)
p-value		0.3929
OR - Odds Ratio (tofersen/placebo)		3.78
SE of log (OR)		1.533
95% CI		(0.187, 76.365)
p-value		0.3857
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.048
95% CI		(-0.041, 0.148)
p-value		0.2651

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by age at first dose - safety population

>= 55 years

	placebo (N=13)	tofersen 100 mg (N=26)
Number of subjects with at least one adverse event leading to drug discontinuation	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.56
SE of log (RR)		1.599
95% CI		(0.068, 35.754)
p-value		0.7824
OR - Odds Ratio (tofersen/placebo)		1.59
SE of log (OR)		1.667
95% CI		(0.060, 41.700)
p-value		0.7814
ARR - Absolute Risk Reduction (tofersen/placebo)		0.02
SE of ARR		0.066
95% CI		(-0.110, 0.150)
p-value		0.7649

Source: biib067/valueaccess/amnog/t-ae-disc-event-sgrp.sas:t-ae-disc-event-sgrp-adose.rtf **Data Cutoff:** 16JUL2021 **Run Date:** 30MAR2023

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by system organ class: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

233AS101 Part C: Number of subjects with at least one adverse event leading to drug discontinuation by preferred term: treatment by subgroup interaction – safety population

No significant difference in main analysis = no subgroup analysis needed.

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233AS101 and 233AS102 ISE: Subject accountability for pooled group CL - by population

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	CL mITT: 233AS101 Part C and 233AS102 (Part C subjects)		CL non mITT: 233AS101 Part C and 233AS102 (Part C subjects)		CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=21)	**Early-start tofersen 100 mg (N=39)**	**placebo + delayed-start tofersen 100 mg (N=15)**	**Early-start tofersen 100 mg (N=33)**	**placebo + delayed-start tofersen 100 mg (N=36)**	**Early-start tofersen 100 mg (N=72)**
Number (%) of subjects	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)
Dosed in 233AS101	21 (100)	39 (100)	15 (100)	33 (100)	36 (100)	72 (100)
Dosed in 233AS102	19 (90)	33 (85)	13 (87)	30 (91)	32 (89)	63 (88)
Completed 233AS101 but not enrolled in 233AS102	0	0	1 (6.7)	1 (3.0)	1 (2.8)	1 (1.4)
Ongoing in 233AS102 at interim	10 (47.6)	21 (53.8)	8 (53.3)	28 (84.8)	18 (50.0)	49 (68.1)
Length of follow-up since 233AS101 baseline (a)						
>= 28 weeks	19 (90.5)	34 (87.2)	14 (93.3)	31 (93.9)	33 (91.7)	65 (90.3)
>= 52 weeks	15 (71.4)	29 (74.4)	13 (86.7)	30 (90.9)	28 (77.8)	59 (81.9)
>= 76 weeks	3 (14.3)	14 (35.9)	10 (66.7)	30 (90.9)	13 (36.1)	44 (61.1)
>= 100 weeks	2 (9.5)	7 (17.9)	10 (66.7)	30 (90.9)	12 (33.3)	37 (51.4)
>= 124 weeks	1 (4.8)	4 (10.3)	5 (33.3)	19 (57.6)	6 (16.7)	23 (31.9)

(a) Counts under the length of follow-up since 233AS101 baseline are based on actual observed data of the subjects up to their last assessment in the study. Subjects who died, withdrew or did not roll over to the extension study 233AS102 before the given threshold will be excluded from the counts.

Source: biib067/ise/ise-bla2/t-bl-acct-pl-cl.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Subject accountability for pooled group CL - by population

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	CL mITT: 233AS101 Part C and 233AS102 (Part C subjects)		CL non mITT: 233AS101 Part C and 233AS102 (Part C subjects)		CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=21)	Early-start tofersen 100 mg (N=39)	placebo + delayed-start tofersen 100 mg (N=15)	Early-start tofersen 100 mg (N=33)	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Discontinued treatment	11 (52.4)	18 (46.2)	7 (46.7)	5 (15.2)	18 (50.0)	23 (31.9)
Adverse event	[redacted]		[redacted]		[redacted]	
Lost to follow-up			0	0		
Consent withdrawn			3 (20.0)	3 (9.1)		
Investigator decision			0	0		
Death			[redacted]			
Non-compliance with study protocol			0	0		
Pregnancy			0	0		
Disease progression			0	0		
Other			1 (6.7)	1 (3.0)		
Withdrew from study	11 (52.4)	18 (46.2)	6 (40.0)	4 (12.1)	17 (47.2)	22 (30.6)
Adverse event	[redacted]		[redacted]		[redacted]	
Lost to follow-up			0	0		
Consent withdrawn			3 (20.0)	2 (6.1)		
Investigator decision			0	0		
Death			[redacted]			
Non-compliance with study protocol			0	0		
Pregnancy			0	0		
Disease progression			[redacted]			
Other			0	0		
Death including vital status data	8 (38.1)	11 (28.2)	3 (20.0)	1 (3.0)	11 (30.6)	12 (16.7)

(a) Counts under the length of follow-up since 233AS101 baseline are based on actual observed data of the subjects up to their last assessment in the study. Subjects who died, withdrew or did not roll over to the extension study 233AS102 before the given threshold will be excluded from the counts.

Source: biib067/ise/ise-bla2/t-bl-acct-pl-cl.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with an event of death or permanent ventilation	8 (22.2)	12 (16.7)
Death	4 (11.1)	4 (5.6)
Permanent ventilation	4 (11.1)	8 (11.1)
Number of days with ventilation use for at least 22 hours per day		
n	4	8
Mean (SD)	101.50 (82.706)	45.50 (33.415)
Median	98.50	50.50
Q1,Q3	38.00, 165.00	13.50, 71.00
Min, Max	8.0, 201.0	4.0, 90.0
[redacted]		
Number of subjects who were censored	28 (77.8)	60 (83.3)

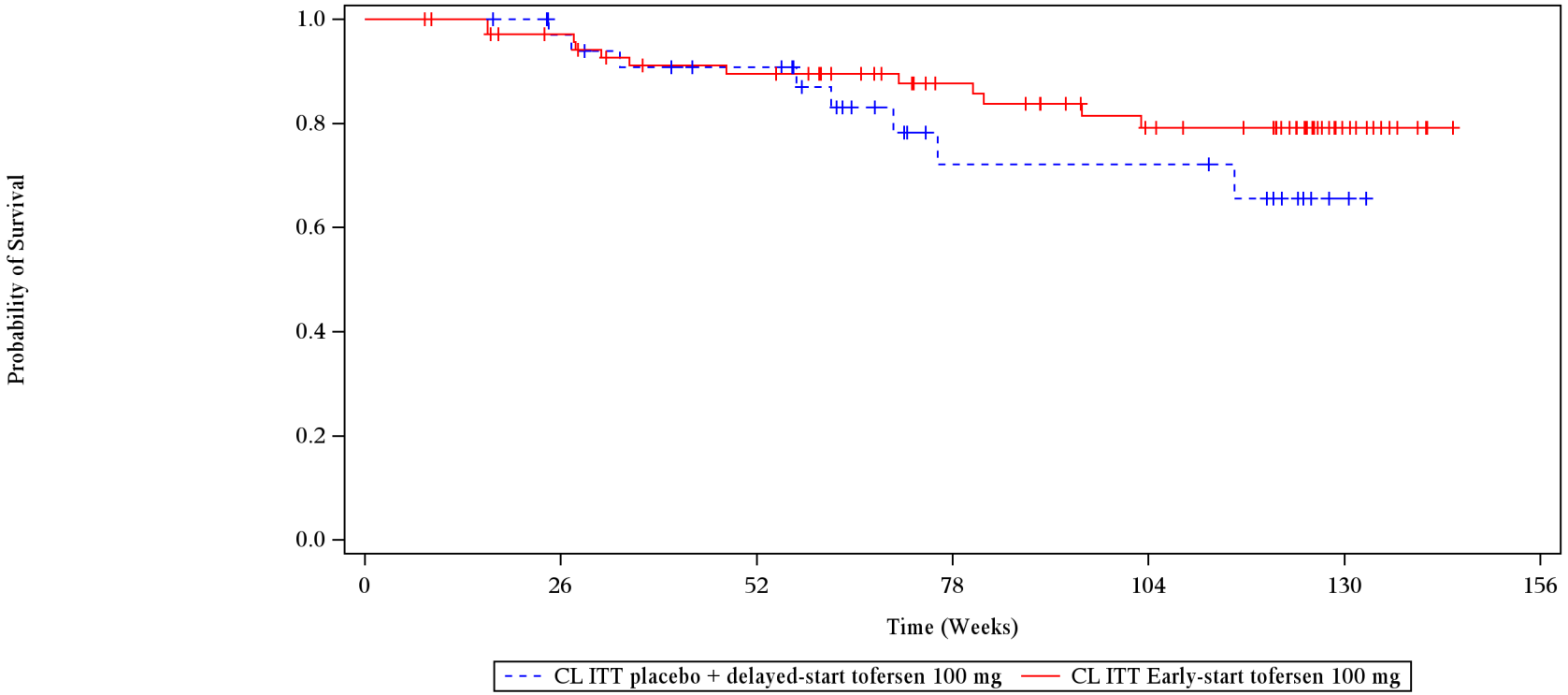
NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla2/t-vafs-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Time to death or permanent ventilation (95% CI) (weeks) (a)		
5th percentile	27.4 (24.4 , 57.3)	28.0 (16.3 , 48.0)
10th percentile	57.3 (24.4 , 70.1)	48.0 (16.3 , 95.1)
25th percentile	76.0 (33.9, NE)	NE (80.7, NE)
50th percentile	NE (76.0, NE)	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects with an event of death or permanent ventilation by		
26 weeks	0.030	0.029
52 weeks	0.092	0.105
78 weeks	0.278	0.123
104 weeks	0.278	0.208
130 weeks	0.344	0.208
p-value (tofersen - placebo) (b)		0.0687
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.2728
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.36 (0.137, 0.941)
p-value (tofersen - placebo) (d)		0.0373

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla2/t-vafs-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death or permanent ventilation for pooled group CL - ITT population



At Risk:

CL ITT placebo + delayed-start tofersen 100 mg	36	32	27	12	12	2
CL ITT Early-start tofersen 100 mg	72	65	57	44	34	11

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/ise/ise-bla2/f-vafs-km-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15MAR2022

233AS101 and 233AS102 ISE: Summary of time to death since 233AS101 baseline for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects who died	6 (16.7)	8 (11.1)
Number of subjects who were censored	30 (83.3)	64 (88.9)
Time to death (95% CI) (weeks)		
5th percentile	57.1 (33.9 , 61.9)	52.1 (16.3 , 82.1)
10th percentile	60.7 (33.9 , 115.4)	82.1 (31.4, NE)
25th percentile	115.4 (57.1, NE)	NE (99.1, NE)
50th percentile	NE (115.4, NE)	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects who died by		
26 weeks	0.000	0.014
52 weeks	0.031	0.046
78 weeks	0.201	0.099
104 weeks	0.201	0.142
130 weeks	0.273	0.142
p-value (tofersen - placebo) (b)		0.0879
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.2827
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.27 (0.084 ,0.890)
p-value (tofersen - placebo) (d)		0.0313

NOTE 1: Time to death as the time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla2/t-surv-sum-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death since 233AS101 baseline for pooled group CL - ITT population

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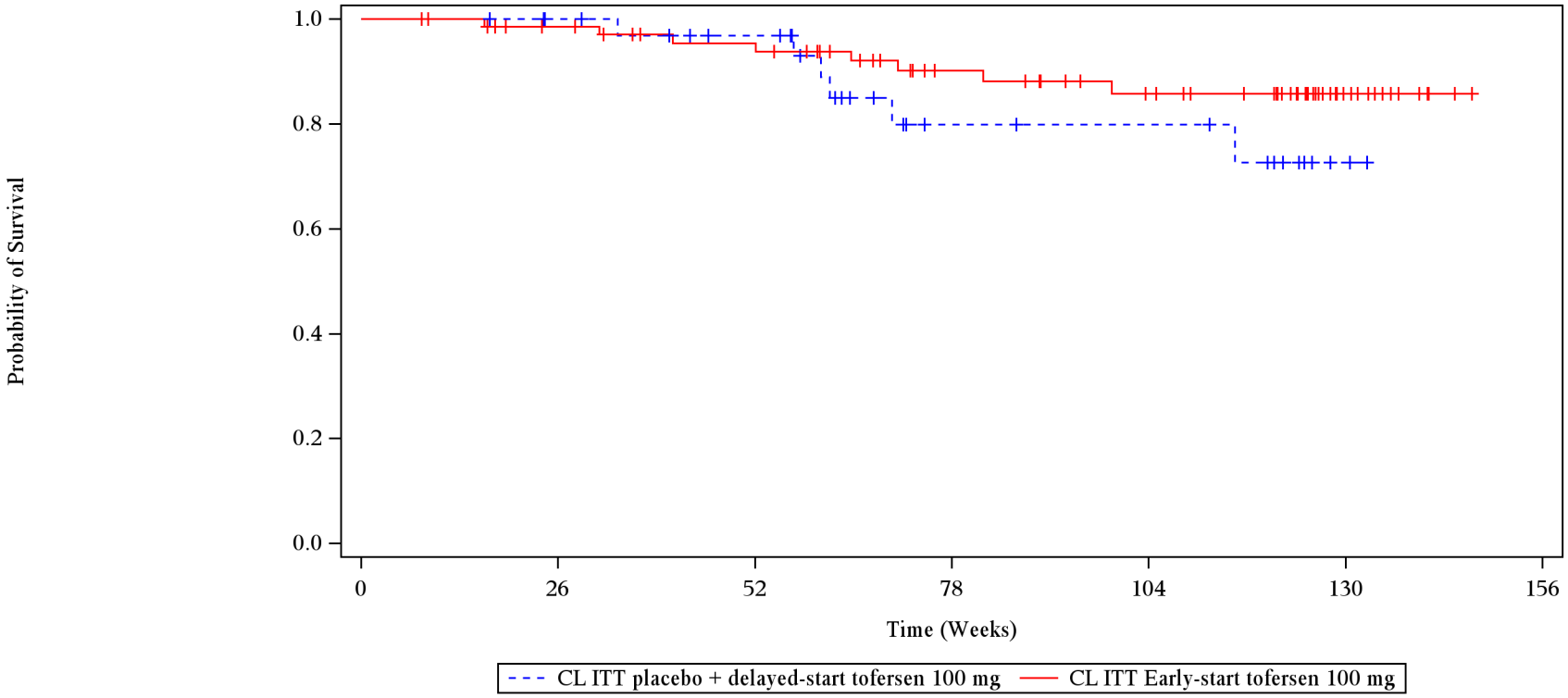

NOTE 1: Time to death is defined as the time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/ise/ise-bla2/f-surv-km-clitt.sas **Run Date:** 11MAR2022

233AS101 and 233AS102 ISE: Summary of time to permanent ventilation adjusting for baseline NfL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects with permanent ventilation	4 (11.1)	8 (11.1)
Number of subjects who were censored	32 (88.9)	64 (88.9)
Time to permanent ventilation (95% CI) (weeks) (a)		
5th percentile	27.4 (NE, 76.0)	35.1 (16.3 , 95.1)
10th percentile	76.0 (24.4, NE)	95.1 (27.7, NE)
25th percentile	NE (57.3, NE)	NE (103.0, NE)
50th percentile	NA	NA
75th percentile	NA	NA

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum-clitt-bpnfl.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 and 233AS102 ISE: Summary of time to permanent ventilation adjusting for baseline NfL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Estimated proportion (a) of subjects with permanent ventilation by		
26 weeks	0.030	0.014
52 weeks	0.061	0.077
78 weeks	0.169	0.077
104 weeks	0.169	0.146
130 weeks	0.169	0.146
p-value (tofersen - placebo) (b)		0.3908
log-rank stratified by randomization factors: p-value (tofersen - placebo) (c)		0.8038
Hazard ratio (tofersen - placebo) and 95% CI (d)		0.46 (0.124, 1.684)
p-value (tofersen - placebo) (d)		0.2389

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog/t-cf-vafsp-sum-clitt-bpnfl.sas **Data Cutoff:** 16JUL2021 **Run Date:** 11JUL2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to permanent ventilation for pooled group CL - ITT population

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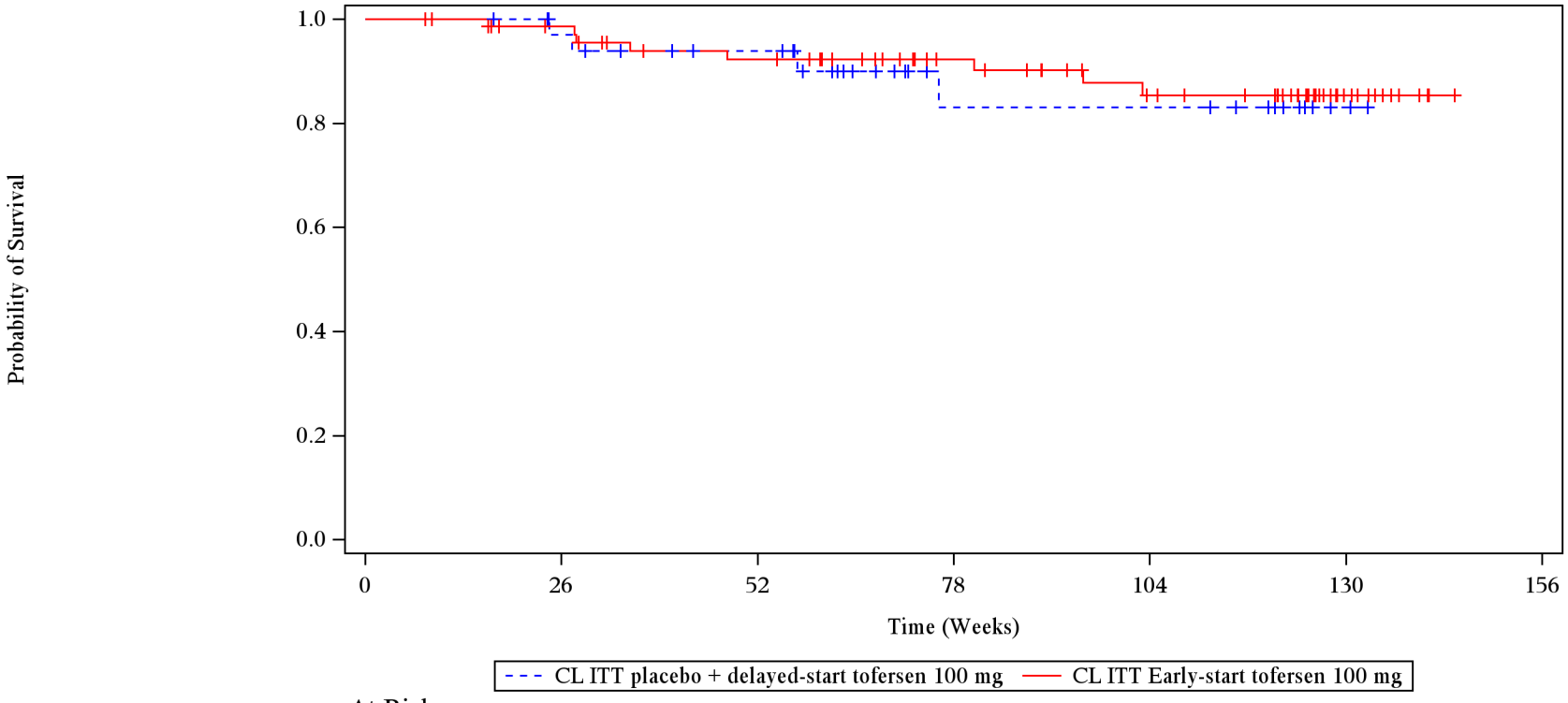

At Risk:

CL ITT placebo + delayed-start tofersen 100 mg	36	32	27	12	12	2	0
CL ITT Early-start tofersen 100 mg	72	65	57	44	34	11	0

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days). Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/valueaccess/amnog/f-surv-km-vafsp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Summary of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with an event	13 (36.1)	18 (25.0)
Death	4 (11.1)	4 (5.6)
Permanent ventilation	4 (11.1)	8 (11.1)
Withdrawal due to disease progression	5 (13.9)	6 (8.3)
Number of subjects who were censored	23 (63.9)	54 (75.0)
Time to event (95% CI) (weeks) (a)		
5th percentile	24.3 (17.0 , 33.9)	17.7 (8.9 , 35.1)
10th percentile	27.4 (17.0 , 55.3)	31.4 (16.3 , 70.9)
25th percentile	61.9 (27.4 , 115.4)	95.1 (48.0, NE)
50th percentile	NE (70.1, NE)	NA
75th percentile	NA	NA

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla2/t-phoc-vafs-wddp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Summary of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Estimated proportion (a) of subjects with an event by		
26 weeks	0.085	0.057
52 weeks	0.173	0.145
78 weeks	0.398	0.195
104 weeks	0.398	0.294
130 weeks	0.453	0.294
p-value (tofersen - placebo) (b)		0.0217
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.1527
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.38 (0.180 ,0.821)
p-value (tofersen - placebo) (d)		0.0135

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla2/t-phoc-vafs-wddp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 22MAR2022

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - by population

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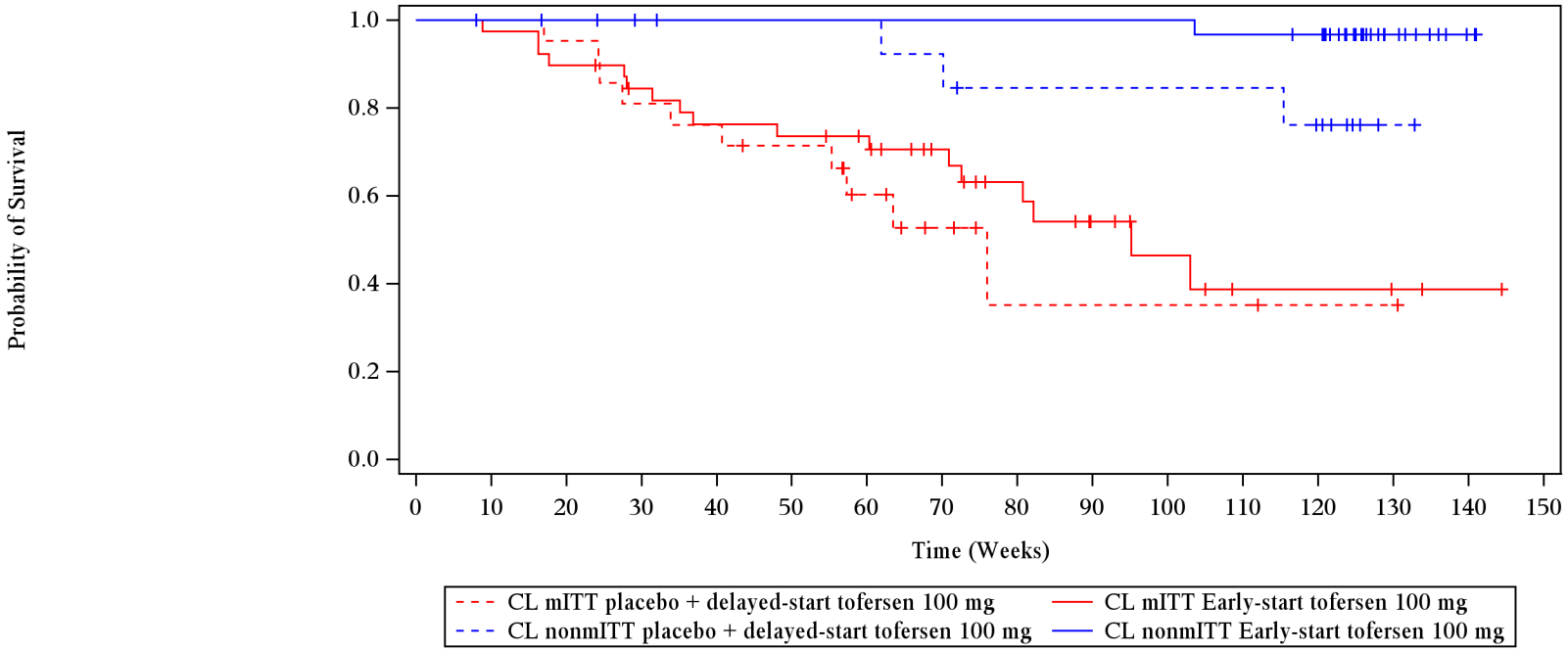

At Risk:

CL mITT placebo + delayed-start tofersen 100 mg	21	18	14	2	2	1
CL mITT Early-start tofersen 100 mg	39	34	27	14	5	2
CL nonmITT placebo + delayed-start tofersen 100 mg	15	14	13	10	10	1
CL nonmITT Early-start tofersen 100 mg	33	31	30	30	29	9

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.

Source: biib067/ise/ise-bla2/f-phoc-vafs-wddp-km-cl12.sas **Data Cutoff:** 16JAN2022 **Run Date:** 15MAR2022

233AS101 and 233AS102 ISE: Summary of time to withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects withdrew due to disease progression	7 (19.4)	8 (11.1)
Number of subjects who were censored	29 (80.6)	64 (88.9)
Time to withdrawal due to disease progression (95% CI) (weeks) (a)		
5th percentile	24.3 (17.0 , 55.3)	35.9 (8.9 , 72.6)
10th percentile	45.9 (17.0 , 86.6)	72.6 (17.7, NE)
25th percentile	86.6 (45.9, NE)	NE (103.6, NE)
50th percentile	NA	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects withdrew due to disease progression by		
26 weeks	0.056	0.043
52 weeks	0.118	0.074
78 weeks	0.192	0.109
104 weeks	0.254	0.134
130 weeks	0.254	0.134
156 weeks	NA	NA
p-value (tofersen - placebo) (b)		0.0794
log-rank stratified by randomization factors: p-value (tofersen - placebo) (c)		0.2829
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.40 (0.139 ,1.167)
p-value (tofersen - placebo) (d)		0.0939

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog/t-cf-vwdp-sum-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Summary of time to withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog/t-cf-vwdp-sum-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to early withdrawal due to disease progression for pooled group CL - ITT population

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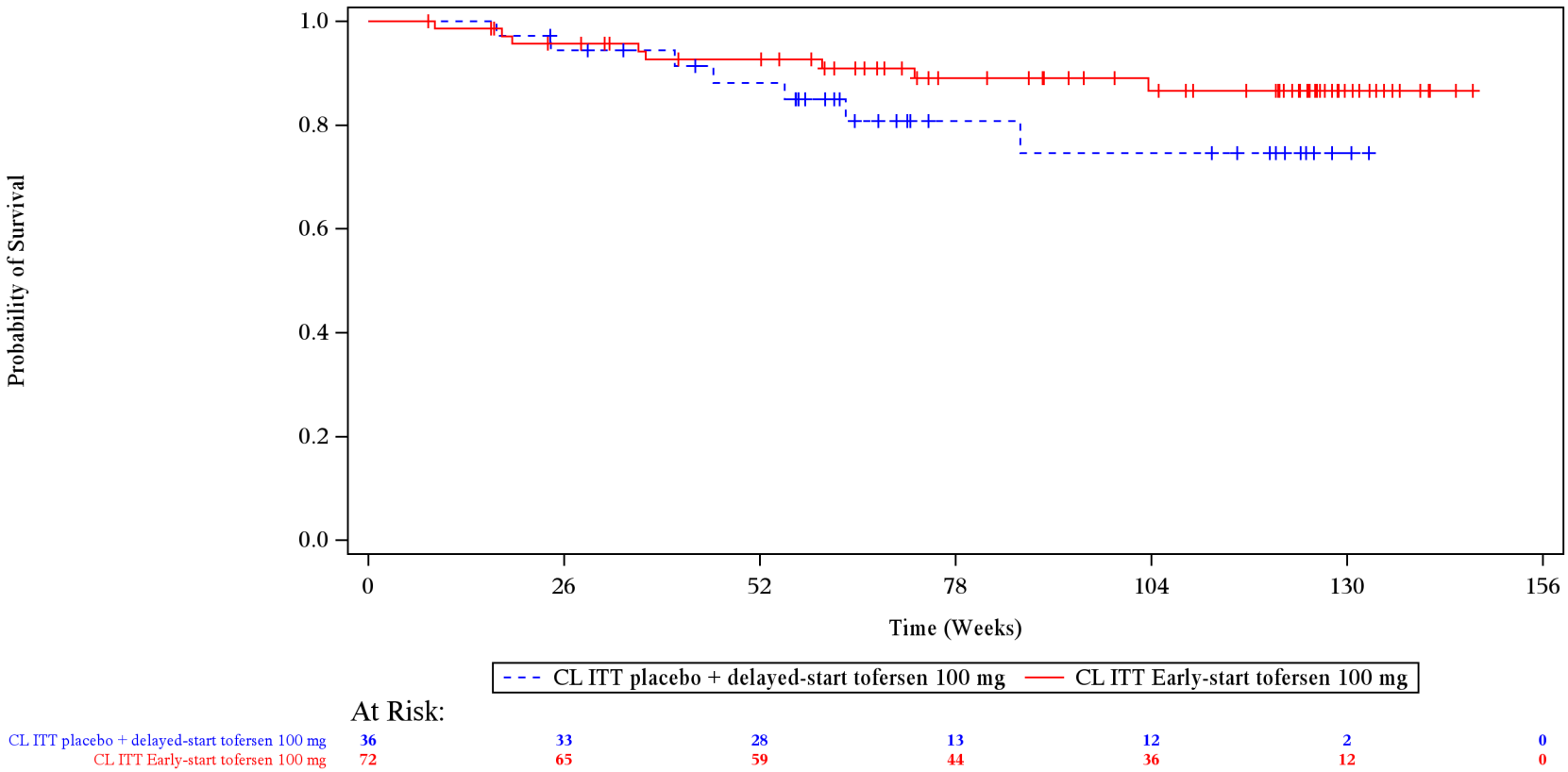

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
NOTE 2: + indicates censored data.
Source: biib067/valueaccess/amnog/f-surv-km-vwdp-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-1.9	-1.4
SE	0.64	0.50
95% CI	(-3.14, -0.64)	(-2.36, -0.39)
LS mean difference (tofersen - placebo)		0.5
SE		0.70
95% CI		(-0.85, 1.89)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.31, 0.50)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 20JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-6.3	-4.2
SE	1.14	0.90
95% CI	(-8.49, -4.02)	(-5.92, -2.40)
LS mean difference (tofersen - placebo)		2.1
SE		1.25
95% CI		(-0.36, 4.54)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.19, 0.65)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 20JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-8.7	-5.7
SE	1.38	1.10
95% CI	(-11.43, -6.01)	(-7.86, -3.57)
LS mean difference (tofersen - placebo)		3.0
SE		1.52
95% CI		(0.03, 5.97)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.16, 0.74)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 20JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-9.5	-6.0
SE	1.50	1.18
95% CI	(-12.47, -6.58)	(-8.29, -3.67)
LS mean difference (tofersen - placebo)		3.5
SE		1.60
95% CI		(0.40, 6.69)
p-value		0.0272
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.15, 0.76)
p-value		0.1915

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 20JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by visit MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-1.6	-1.1
SE	0.58	0.43
95% CI	(-2.78, -0.50)	(-1.98, -0.26)
LS mean difference (tofersen - placebo)		0.5
SE		0.68
95% CI		(-0.83, 1.87)
Week 28		
N	33	63
LS mean change from baseline	-5.9	-3.7
SE	1.06	0.77
95% CI	(-7.98, -3.75)	(-5.22, -2.15)
LS mean difference (tofersen - placebo)		2.2
SE		1.29
95% CI		(-0.39, 4.75)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 23JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by visit MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	29	58
LS mean change from baseline	-8.0	-4.7
SE	1.30	0.94
95% CI	(-10.55, -5.36)	(-6.60, -2.87)
LS mean difference (tofersen - placebo)		3.2
SE		1.58
95% CI		(0.06, 6.38)
Week 52		
N	28	57
LS mean change from baseline	-8.7	-4.9
SE	1.38	0.99
95% CI	(-11.42, -5.90)	(-6.90, -2.96)
LS mean difference (tofersen - placebo)		3.7
SE		1.68
95% CI		(0.37, 7.09)
p-value		0.0302

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALSFRS-R total scores range from 0 to 48. A higher score or a positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 23JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	0.0
SE	0.17	0.13
95% CI	(-0.45, 0.21)	(-0.26, 0.25)
LS mean difference (tofersen - placebo)		0.1
SE		0.18
95% CI		(-0.24, 0.47)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.29, 0.53)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-0.5	-0.6
SE	0.27	0.21
95% CI	(-1.03, 0.04)	(-1.06, -0.22)
LS mean difference (tofersen - placebo)		-0.1
SE		0.30
95% CI		(-0.73, 0.45)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.53, 0.32)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-1.1	-1.2
SE	0.34	0.27
95% CI	(-1.80, -0.45)	(-1.74, -0.68)
LS mean difference (tofersen - placebo)		-0.1
SE		0.38
95% CI		(-0.83, 0.65)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.37)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-1.7	-1.4
SE	0.46	0.38
95% CI	(-2.63, -0.81)	(-2.20, -0.69)
LS mean difference (tofersen - placebo)		0.3
SE		0.51
95% CI		(-0.72, 1.26)
p-value		0.5889
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.43, 0.47)
p-value		0.9388

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.6	-0.6
SE	0.23	0.18
95% CI	(-1.03, -0.12)	(-0.95, -0.23)
LS mean difference (tofersen - placebo)		0.0
SE		0.25
95% CI		(-0.51, 0.49)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.45, 0.36)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-2.0	-1.2
SE	0.38	0.30
95% CI	(-2.79, -1.31)	(-1.83, -0.66)
LS mean difference (tofersen - placebo)		0.8
SE		0.41
95% CI		(-0.01, 1.62)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.12, 0.72)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.4	-1.6
SE	0.44	0.35
95% CI	(-3.27, -1.56)	(-2.25, -0.89)
LS mean difference (tofersen - placebo)		0.8
SE		0.48
95% CI		(-0.10, 1.78)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.18, 0.71)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-2.6	-1.6
SE	0.46	0.36
95% CI	(-3.48, -1.69)	(-2.27, -0.85)
LS mean difference (tofersen - placebo)		1.0
SE		0.49
95% CI		(0.06, 1.99)
p-value		0.0374
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.15, 0.76)
p-value		0.1821

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.7	-0.6
SE	0.24	0.19
95% CI	(-1.16, -0.22)	(-0.93, -0.19)
LS mean difference (tofersen - placebo)		0.1
SE		0.26
95% CI		(-0.38, 0.64)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.34, 0.47)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-2.0	-1.0
SE	0.33	0.26
95% CI	(-2.61, -1.30)	(-1.51, -0.48)
LS mean difference (tofersen - placebo)		1.0
SE		0.36
95% CI		(0.24, 1.67)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.01, 0.84)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.3	-1.3
SE	0.36	0.29
95% CI	(-3.00, -1.58)	(-1.86, -0.73)
LS mean difference (tofersen - placebo)		1.0
SE		0.40
95% CI		(0.21, 1.78)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.01, 0.89)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-2.1	-1.1
SE	0.39	0.30
95% CI	(-2.82, -1.31)	(-1.70, -0.51)
LS mean difference (tofersen - placebo)		1.0
SE		0.42
95% CI		(0.13, 1.79)
p-value		0.0227
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.07, 0.85)
p-value		0.0935

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.5	-0.2
SE	0.35	0.27
95% CI	(-1.17, 0.19)	(-0.77, 0.29)
LS mean difference (tofersen - placebo)		0.3
SE		0.38
95% CI		(-0.48, 1.00)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.29, 0.52)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-1.7	-1.3
SE	0.51	0.40
95% CI	(-2.70, -0.71)	(-2.11, -0.56)
LS mean difference (tofersen - placebo)		0.4
SE		0.55
95% CI		(-0.72, 1.45)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.36, 0.48)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.8	-1.7
SE	0.60	0.48
95% CI	(-4.01, -1.65)	(-2.64, -0.78)
LS mean difference (tofersen - placebo)		1.1
SE		0.66
95% CI		(-0.17, 2.41)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.18, 0.72)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-3.1	-1.9
SE	0.62	0.48
95% CI	(-4.33, -1.91)	(-2.82, -0.93)
LS mean difference (tofersen - placebo)		1.2
SE		0.67
95% CI		(-0.06, 2.55)
p-value		0.0623
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.17, 0.73)
p-value		0.2266

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-0.1	0.1
SE	0.15	0.12
95% CI	(-0.38, 0.24)	(-0.18, 0.28)
LS mean difference (tofersen - placebo)		0.1
SE		0.18
95% CI		(-0.24, 0.48)
Week 28		
N	33	63
LS mean change from baseline	-0.3	-0.5
SE	0.25	0.18
95% CI	(-0.82, 0.18)	(-0.82, -0.10)
LS mean difference (tofersen - placebo)		-0.1
SE		0.30
95% CI		(-0.74, 0.46)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	29	58
LS mean change from baseline	-0.8	-0.9
SE	0.32	0.23
95% CI	(-1.40, -0.11)	(-1.40, -0.47)
LS mean difference (tofersen - placebo)		-0.2
SE		0.40
95% CI		(-0.96, 0.62)
Week 52		
N	28	57
LS mean change from baseline	-1.3	-1.2
SE	0.42	0.30
95% CI	(-2.16, -0.49)	(-1.77, -0.58)
LS mean difference (tofersen - placebo)		0.1
SE		0.51
95% CI		(-0.87, 1.17)
p-value		0.7704

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-0.4	-0.5
SE	0.22	0.16
95% CI	(-0.87, -0.02)	(-0.78, -0.14)
LS mean difference (tofersen - placebo)		0.0
SE		0.26
95% CI		(-0.52, 0.49)
Week 28		
N	33	63
LS mean change from baseline	-2.0	-1.1
SE	0.35	0.25
95% CI	(-2.72, -1.34)	(-1.63, -0.63)
LS mean difference (tofersen - placebo)		0.9
SE		0.42
95% CI		(0.06, 1.74)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	29	58
LS mean change from baseline	-2.3	-1.4
SE	0.41	0.29
95% CI	(-3.13, -1.52)	(-1.96, -0.80)
LS mean difference (tofersen - placebo)		0.9
SE		0.49
95% CI		(-0.03, 1.92)
Week 52		
N	28	57
LS mean change from baseline	-2.5	-1.4
SE	0.42	0.30
95% CI	(-3.32, -1.66)	(-1.94, -0.76)
LS mean difference (tofersen - placebo)		1.1
SE		0.50
95% CI		(0.14, 2.14)
p-value		0.0264

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-0.6	-0.5
SE	0.22	0.17
95% CI	(-1.05, -0.17)	(-0.81, -0.15)
LS mean difference (tofersen - placebo)		0.1
SE		0.26
95% CI		(-0.39, 0.65)
Week 28		
N	33	63
LS mean change from baseline	-2.0	-1.0
SE	0.31	0.22
95% CI	(-2.64, -1.42)	(-1.41, -0.51)
LS mean difference (tofersen - placebo)		1.1
SE		0.37
95% CI		(0.33, 1.80)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	29	58
LS mean change from baseline	-2.2	-1.1
SE	0.34	0.24
95% CI	(-2.87, -1.53)	(-1.61, -0.64)
LS mean difference (tofersen - placebo)		1.1
SE		0.41
95% CI		(0.27, 1.89)
Week 52		
N	28	57
LS mean change from baseline	-1.9	-0.9
SE	0.36	0.26
95% CI	(-2.65, -1.21)	(-1.42, -0.39)
LS mean difference (tofersen - placebo)		1.0
SE		0.44
95% CI		(0.16, 1.90)
p-value		0.0205

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-0.7	-0.4
SE	0.32	0.24
95% CI	(-1.29, -0.03)	(-0.86, 0.08)
LS mean difference (tofersen - placebo)		0.3
SE		0.38
95% CI		(-0.48, 1.02)
Week 28		
N	33	63
LS mean change from baseline	-1.6	-1.2
SE	0.45	0.33
95% CI	(-2.48, -0.69)	(-1.86, -0.56)
LS mean difference (tofersen - placebo)		0.4
SE		0.55
95% CI		(-0.71, 1.46)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by visit MMRM analysis for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	29	58
LS mean change from baseline	-2.6	-1.4
SE	0.55	0.40
95% CI	(-3.66, -1.47)	(-2.19, -0.61)
LS mean difference (tofersen - placebo)		1.2
SE		0.67
95% CI		(-0.17, 2.50)
Week 52		
N	28	57
LS mean change from baseline	-2.8	-1.6
SE	0.57	0.41
95% CI	(-3.97, -1.69)	(-2.38, -0.75)
LS mean difference (tofersen - placebo)		1.3
SE		0.69
95% CI		(-0.12, 2.65)
p-value		0.0722

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MMRM = mixed model for repeated measures.
Source: biib067/valueaccess/amnog/t-cf-alsf-d-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSFRS-R total score >= 15% at Week 52 using MI for pooled group CL - ITT population

	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Average proportion of subjects with worsening in ALSFRS-R total score > = 15%	42.3	29.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.62
SE of log(RR)		0.250
95% CI		(0.378, 1.006)
p-value		0.0529
Adjusted OR - Odds Ratio (tofersen/placebo)		0.36
SE of log(OR)		0.571
95% CI		(0.117, 1.102)
p-value		0.0735
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.13
SE of ARR		0.103
95% CI		(-0.328, 0.074)
p-value		0.2167

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 03JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	35.4	26.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.68
SE of log(RR)		0.292
95% CI		(0.383, 1.203)
p-value		0.1847
Adjusted OR - Odds Ratio (tofersen/placebo)		0.49
SE of log(OR)		0.562
95% CI		(0.162, 1.471)
p-value		0.2026
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.103
95% CI		(-0.287, 0.116)
p-value		0.4045

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	46.5	37.9
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.221
95% CI		(0.481, 1.144)
p-value		0.1770
Adjusted OR - Odds Ratio (tofersen/placebo)		0.53
SE of log(OR)		0.498
95% CI		(0.198, 1.394)
p-value		0.1964
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.105
95% CI		(-0.291, 0.118)
p-value		0.4079

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	42.4	33.6
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.249
95% CI		(0.447, 1.187)
p-value		0.2041
Adjusted OR - Odds Ratio (tofersen/placebo)		0.56
SE of log(OR)		0.479
95% CI		(0.217, 1.420)
p-value		0.2194
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.09
SE of ARR		0.103
95% CI		(-0.289, 0.113)
p-value		0.3916

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSFRS-R domain score > = 15%	47.3	31.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.60
SE of log(RR)		0.237
95% CI		(0.377, 0.956)
p-value		0.0315
Adjusted OR - Odds Ratio (tofersen/placebo)		0.36
SE of log(OR)		0.513
95% CI		(0.130, 0.974)
p-value		0.0444
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.16
SE of ARR		0.103
95% CI		(-0.362, 0.043)
p-value		0.1218

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSFRS-R total score >= 15% at Week 52 using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSFRS-R total score > = 15%	[redacted]	
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		1.397
95% CI		(0.036, 8.635)
p-value		0.6766
Adjusted OR - Odds Ratio (tofersen/placebo)		0.55
SE of log(OR)		1.431
95% CI		(0.033, 9.121)
p-value		0.6780
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.023
95% CI		(-0.049, 0.039)
p-value		0.8282

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

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ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	0.1	1.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.15
SE of log(RR)		1.200
95% CI		(0.110, 12.113)
p-value		0.9058
Adjusted OR - Odds Ratio (tofersen/placebo)		1.16
SE of log(OR)		1.244
95% CI		(0.101, 13.282)
p-value		0.9057
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.028
95% CI		(-0.044, 0.064)
p-value		0.7211

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 03JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

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ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	5.6	6.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.33
SE of log(RR)		0.817
95% CI		(0.267, 6.579)
p-value		0.7298
Adjusted OR - Odds Ratio (tofersen/placebo)		1.38
SE of log(OR)		0.917
95% CI		(0.228, 8.301)
p-value		0.7270
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.049
95% CI		(-0.088, 0.104)
p-value		0.8696

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 03JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	5.6	5.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.15
SE of log(RR)		0.812
95% CI		(0.234, 5.635)
p-value		0.8650
Adjusted OR - Odds Ratio (tofersen/placebo)		1.16
SE of log(OR)		0.873
95% CI		(0.209, 6.409)
p-value		0.8672
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.047
95% CI		(-0.091, 0.095)
p-value		0.9649

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 03JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSFRS-R domain score >= 15% at Week 52 using MI - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSFRS-R domain score > = 15%	6.0	6.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.16
SE of log(RR)		0.858
95% CI		(0.215, 6.214)
p-value		0.8658
Adjusted OR - Odds Ratio (tofersen/placebo)		1.16
SE of log(OR)		0.893
95% CI		(0.202, 6.697)
p-value		0.8647
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.051
95% CI		(-0.093, 0.107)
p-value		0.8938

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised.
Source: biib067/valueaccess/amnog/t-cf-als-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 03JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	35 (97.2)	64 (88.9)
Number of imputed values per imputation	1 (2.8)	8 (11.1)
LS mean change from baseline	-0.16	-0.11
SE	0.052	0.041
95% CI	(-0.261, -0.056)	(-0.196, -0.033)
LS mean difference (tofersen - placebo)		0.04
SE		0.057
95% CI		(-0.069, 0.156)
Hedge's g standardized mean difference (tofersen - placebo)		0.14
95% CI		(-0.277, 0.548)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 25JUN2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	27 (75.0)	58 (80.6)
Number of imputed values per imputation	9 (25.0)	14 (19.4)
LS mean change from baseline	-0.32	-0.23
SE	0.064	0.049
95% CI	(-0.442, -0.191)	(-0.324, -0.134)
LS mean difference (tofersen - placebo)		0.09
SE		0.070
95% CI		(-0.051, 0.225)
Hedge's g standardized mean difference (tofersen - placebo)		0.21
95% CI		(-0.249, 0.666)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 25JUN2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 40		
Number of observations per imputation	24 (66.7)	47 (65.3)
Number of imputed values per imputation	12 (33.3)	25 (34.7)
LS mean change from baseline	-0.48	-0.19
SE	0.094	0.072
95% CI	(-0.667, -0.300)	(-0.334, -0.054)
LS mean difference (tofersen - placebo)		0.29
SE		0.101
95% CI		(0.091, 0.488)
Hedge's g standardized mean difference (tofersen - placebo)		0.57
95% CI		(0.066, 1.068)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 25JUN2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 52		
Number of observations per imputation	25 (69.4)	42 (58.3)
Number of imputed values per imputation	11 (30.6)	30 (41.7)
LS mean change from baseline	-0.45	-0.17
SE	0.109	0.090
95% CI	(-0.667, -0.240)	(-0.349, 0.006)
LS mean difference (tofersen - placebo)		0.28
SE		0.120
95% CI		(0.047, 0.517)
p-value		0.0186
Hedge's g standardized mean difference (tofersen - placebo)		0.51
95% CI		(0.002, 1.007)
p-value		0.0492

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 25JUN2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	35	64
LS mean change from baseline	-0.2	-0.1
SE	0.05	0.04
95% CI	(-0.26, -0.06)	(-0.19, -0.04)
LS mean difference (tofersen - placebo)		0.0
SE		0.06
95% CI		(-0.07, 0.15)
Week 28		
N	27	58
LS mean change from baseline	-0.3	-0.2
SE	0.06	0.04
95% CI	(-0.41, -0.18)	(-0.29, -0.12)
LS mean difference (tofersen - placebo)		0.1
SE		0.07
95% CI		(-0.04, 0.23)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-mega-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
N	24	47
LS mean change from baseline	-0.4	-0.1
SE	0.09	0.06
95% CI	(-0.61, -0.27)	(-0.28, -0.02)
LS mean difference (tofersen - placebo)		0.3
SE		0.10
95% CI		(0.08, 0.50)
Week 52		
N	25	42
LS mean change from baseline	-0.4	-0.2
SE	0.09	0.07
95% CI	(-0.61, -0.23)	(-0.31, -0.02)
LS mean difference (tofersen - placebo)		0.3
SE		0.12
95% CI		(0.02, 0.48)
p-value		0.0321

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-mega-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	34 (94.4)	59 (81.9)
Number of imputed values per imputation	2 (5.6)	13 (18.1)
LS mean change from baseline	-6.9	-3.2
SE	1.76	1.38
95% CI	(-10.32, -3.42)	(-5.95, -0.53)
LS mean difference (tofersen - placebo)		3.6
SE		1.95
95% CI		(-0.18, 7.45)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.16, 0.69)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	25 (69.4)	52 (72.2)
Number of imputed values per imputation	11 (30.6)	20 (27.8)
LS mean change from baseline	-14.9	-7.0
SE	3.10	2.36
95% CI	(-20.99, -8.82)	(-11.66, -2.39)
LS mean difference (tofersen - placebo)		7.9
SE		3.41
95% CI		(1.21, 14.56)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.12, 0.84)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	20 (55.6)	39 (54.2)
Number of imputed values per imputation	16 (44.4)	33 (45.8)
LS mean change from baseline	-20.5	-9.1
SE	3.46	2.66
95% CI	(-27.25, -13.66)	(-14.31, -3.86)
LS mean difference (tofersen - placebo)		11.4
SE		3.79
95% CI		(3.93, 18.81)
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.08, 1.01)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 52		
Number of observations per imputation	20 (55.6)	38 (52.8)
Number of imputed values per imputation	16 (44.4)	34 (47.2)
LS mean change from baseline	-18.6	-9.4
SE	3.45	2.79
95% CI	(-25.38, -11.84)	(-14.93, -3.97)
LS mean difference (tofersen - placebo)		9.2
SE		3.79
95% CI		(1.72, 16.60)
p-value		0.0159
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.18, 0.91)
p-value		0.1940

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point MMRM analysis for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	34	59
LS mean change from baseline	-6.2	-2.5
SE	1.65	1.26
95% CI	(-9.50, -2.95)	(-5.02, -0.03)
LS mean difference (tofersen - placebo)		3.7
SE		1.89
95% CI		(-0.06, 7.45)
Week 28		
N	25	52
LS mean change from baseline	-12.9	-5.0
SE	2.88	2.06
95% CI	(-18.66, -7.20)	(-9.06, -0.86)
LS mean difference (tofersen - placebo)		8.0
SE		3.45
95% CI		(1.10, 14.83)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI. The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point MMRM analysis for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	20	39
LS mean change from baseline	-18.1	-6.7
SE	3.13	2.25
95% CI	(-24.34, -11.88)	(-11.22, -2.27)
LS mean difference (tofersen - placebo)		11.4
SE		3.76
95% CI		(3.87, 18.86)
Week 52		
N	20	38
LS mean change from baseline	-18.1	-8.0
SE	3.15	2.26
95% CI	(-24.34, -11.82)	(-12.52, -3.52)
LS mean difference (tofersen - placebo)		10.1
SE		3.78
95% CI		(2.52, 17.60)
p-value		0.0096

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI. The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog/t-cf-svc-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	35 (97.2)	65 (90.3)
Number of imputed values per imputation	1 (2.8)	7 (9.7)
LS mean change from baseline	-6.1	-4.4
SE	2.44	1.92
95% CI	(-10.86, -1.31)	(-8.20, -0.67)
LS mean difference (tofersen - placebo)		1.7
SE		2.66
95% CI		(-3.57, 6.87)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.21, 0.61)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	-13.5	-7.6
SE	3.15	2.45
95% CI	(-19.67, -7.32)	(-12.44, -2.84)
LS mean difference (tofersen - placebo)		5.9
SE		3.46
95% CI		(-0.92, 12.64)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.11, 0.76)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	28 (77.8)	50 (69.4)
Number of imputed values per imputation	8 (22.2)	22 (30.6)
LS mean change from baseline	-15.2	-8.9
SE	3.37	2.62
95% CI	(-21.79, -8.59)	(-14.06, -3.78)
LS mean difference (tofersen - placebo)		6.3
SE		3.65
95% CI		(-0.89, 13.43)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.12, 0.82)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	26 (72.2)	48 (66.7)
Number of imputed values per imputation	10 (27.8)	24 (33.3)
LS mean change from baseline	-12.9	-7.0
SE	3.53	2.71
95% CI	(-19.78, -5.94)	(-12.33, -1.69)
LS mean difference (tofersen - placebo)		5.9
SE		3.77
95% CI		(-1.54, 13.25)
p-value		0.1209
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.15, 0.82)
p-value		0.1718

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	35	65
LS mean change from baseline	-6.1	-4.5
SE	2.38	1.85
95% CI	(-10.78, -1.36)	(-8.13, -0.81)
LS mean difference (tofersen - placebo)		1.6
SE		2.66
95% CI		(-3.67, 6.89)
Week 28		
N	31	61
LS mean change from baseline	-13.0	-7.0
SE	3.05	2.28
95% CI	(-19.11, -6.99)	(-11.56, -2.52)
LS mean difference (tofersen - placebo)		6.0
SE		3.56
95% CI		(-1.07, 13.08)

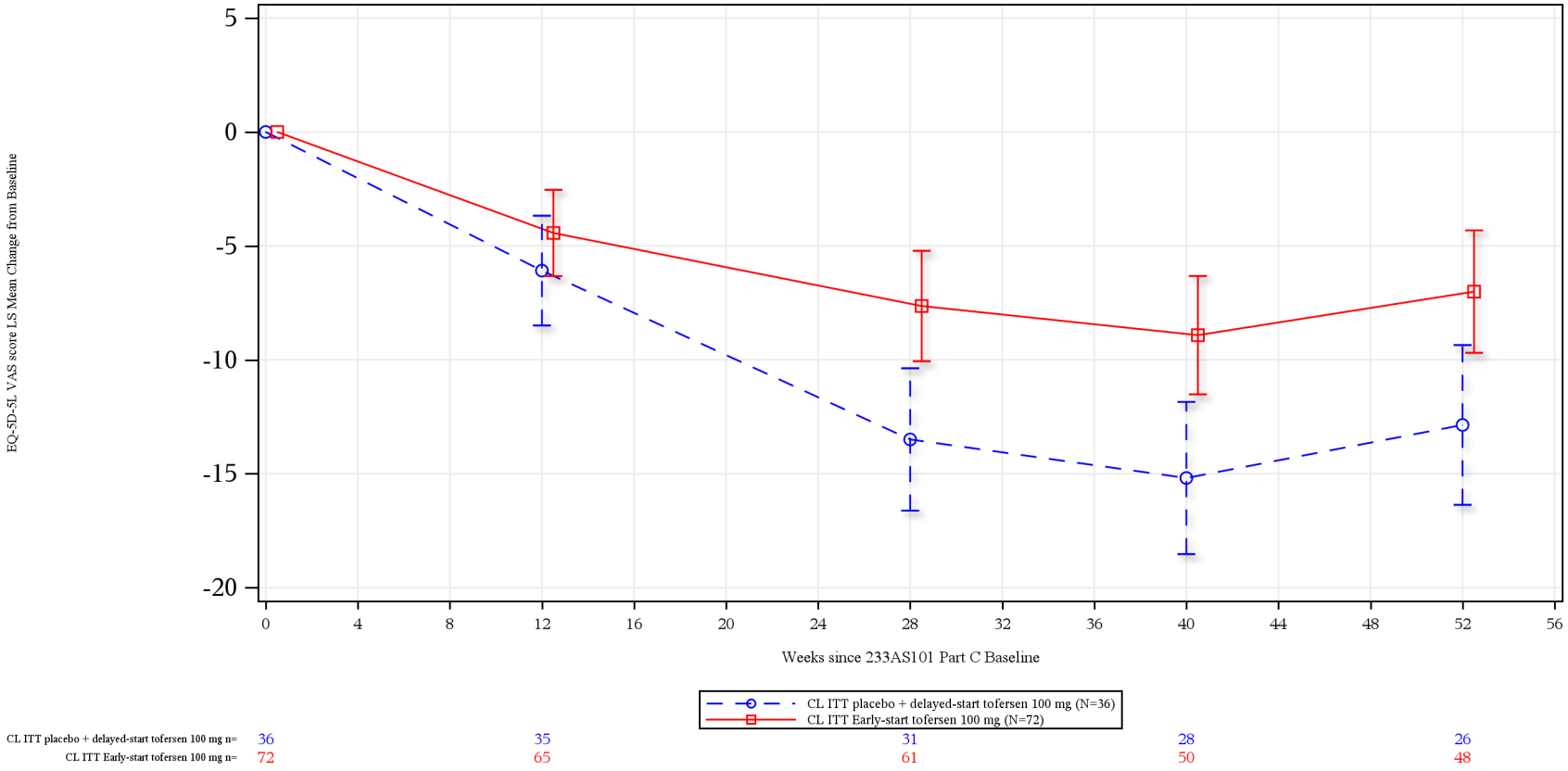
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: EQ-5D-5L VAS score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	28	50
LS mean change from baseline	-14.1	-7.6
SE	3.16	2.37
95% CI	(-20.38, -7.84)	(-12.32, -2.90)
LS mean difference (tofersen - placebo)		6.5
SE		3.70
95% CI		(-0.88, 13.87)
Week 52		
N	26	48
LS mean change from baseline	-12.7	-6.8
SE	3.26	2.44
95% CI	(-19.17, -6.21)	(-11.68, -1.99)
LS mean difference (tofersen - placebo)		5.9
SE		3.83
95% CI		(-1.77, 13.49)
p-value		0.1305

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-eq5vas-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Line plot of EQ-5D-5L VAS score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population



CL ITT placebo + delayed-start tofersen 100 mg n=	36	35	31	28	26
CL ITT Early-start tofersen 100 mg n=	72	65	61	50	48

Footnotes are displayed on last page.

Source: biib067/ise/ise-bla2/f-cf-eq5vas-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31MAR2022

233AS101 and 233AS102 ISE: Line plot of EQ-5D-5L VAS score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline EQ-5D-5L VAS score, and use of riluzole or edaravone.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla2/f-cf-eq5vas-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31MAR2022

233AS101 and 233AS102 ISE: Summary of proportion of worsening in EQ-5D VAS >= 15% at Week 52 using MI for pooled group CL - ITT population

	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Average proportion of subjects with worsening in EQ-5D VAS > = 15%	39.0	24.0
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		0.312
95% CI		(0.304, 1.036)
p-value		0.0647
Adjusted OR - Odds Ratio (tofersen/placebo)		0.40
SE of log(OR)		0.509
95% CI		(0.148, 1.089)
p-value		0.0731
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.15
SE of ARR		0.101
95% CI		(-0.348, 0.047)
p-value		0.1351

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in EQ-5D VAS >= 15% at Week 52 using MI for pooled group CL - ITT population

	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Average proportion of subjects with improvement in EQ-5D VAS > = 15%	2.8	7.8
Adjusted RR - Relative Risk (tofersen/placebo)		2.85
SE of log(RR)		1.128
95% CI		(0.313, 26.036)
p-value		0.3523
Adjusted OR - Odds Ratio (tofersen/placebo)		2.99
SE of log(OR)		1.146
95% CI		(0.317, 28.248)
p-value		0.3390
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.045
95% CI		(-0.038, 0.138)
p-value		0.2628

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: EQ-5D-5L = EuroQoL descriptive system of health-related quality of life states consisting of 5 dimensions, each of which can take 1 of 5 responses (questionnaire); VAS = visual analogue scales.
Source: biib067/valueaccess/amnog/t-cf-eq5d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	35 (97.2)	66 (91.7)
Number of imputed values per imputation	1 (2.8)	6 (8.3)
LS mean change from baseline	1.7	0.1
SE	1.88	1.47
95% CI	(-1.95, 5.43)	(-2.74, 3.02)
LS mean difference (tofersen - placebo)		-1.6
SE		2.05
95% CI		(-5.61, 2.41)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.30)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	6.5	3.8
SE	2.34	1.82
95% CI	(1.87, 11.04)	(0.27, 7.42)
LS mean difference (tofersen - placebo)		-2.6
SE		2.55
95% CI		(-7.60, 2.38)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.58, 0.29)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	28 (77.8)	50 (69.4)
Number of imputed values per imputation	8 (22.2)	22 (30.6)
LS mean change from baseline	2.7	3.6
SE	2.22	1.79
95% CI	(-1.65, 7.07)	(0.13, 7.15)
LS mean difference (tofersen - placebo)		0.9
SE		2.46
95% CI		(-3.89, 5.75)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.35, 0.58)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 52		
Number of observations per imputation	26 (72.2)	49 (68.1)
Number of imputed values per imputation	10 (27.8)	23 (31.9)
LS mean change from baseline	5.1	1.3
SE	2.44	1.95
95% CI	(0.35, 9.93)	(-2.50, 5.13)
LS mean difference (tofersen - placebo)		-3.8
SE		2.65
95% CI		(-9.03, 1.38)
p-value		0.1493
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.73, 0.22)
p-value		0.2941

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 27JUN2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	35	66
LS mean change from baseline	1.2	-0.3
SE	1.85	1.44
95% CI	(-2.44, 4.91)	(-3.15, 2.56)
LS mean difference (tofersen - placebo)		-1.5
SE		2.06
95% CI		(-5.61, 2.55)
Week 28		
N	31	61
LS mean change from baseline	5.5	3.0
SE	2.29	1.72
95% CI	(0.93, 9.99)	(-0.37, 6.44)
LS mean difference (tofersen - placebo)		-2.4
SE		2.63
95% CI		(-7.65, 2.80)

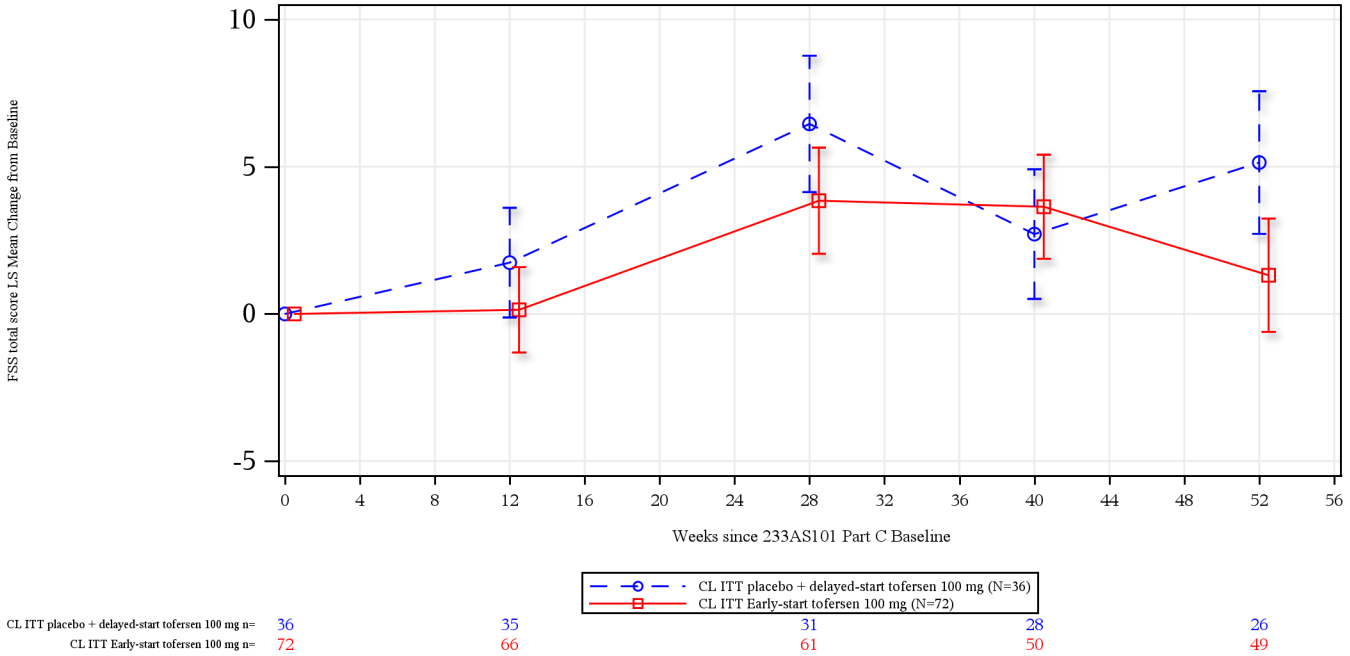
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
N	28	50
LS mean change from baseline	1.6	2.8
SE	2.23	1.70
95% CI	(-2.80, 6.06)	(-0.55, 6.19)
LS mean difference (tofersen - placebo)		1.2
SE		2.57
95% CI		(-3.92, 6.30)
Week 52		
N	26	49
LS mean change from baseline	4.8	1.0
SE	2.38	1.79
95% CI	(0.11, 9.56)	(-2.53, 4.57)
LS mean difference (tofersen - placebo)		-3.8
SE		2.75
95% CI		(-9.28, 1.65)
p-value		0.1690

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less fatigue in everyday life.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-fss-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Line plot of FSS total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population



NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla2/f-cf-fss-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31MAR2022

233AS101 and 233AS102 ISE: Summary of proportion of worsening in FSS total score >= 15% at Week 52 using MI for pooled group CL - ITT population

Page: 1 of 1

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in FSS total score > = 15%	33.6	25.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.73
SE of log(RR)		0.339
95% CI		(0.376, 1.423)
p-value		0.3567
Adjusted OR - Odds Ratio (tofersen/placebo)		0.63
SE of log(OR)		0.509
95% CI		(0.232, 1.707)
p-value		0.3629
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.08
SE of ARR		0.104
95% CI		(-0.282, 0.125)
p-value		0.4504

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 16JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in FSS total score >= 15% at Week 52 using MI for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in FSS total score > = 15%	11.4	15.5
Adjusted RR - Relative Risk (tofersen/placebo)		1.39
SE of log(RR)		0.581
95% CI		(0.446, 4.346)
p-value		0.5692
Adjusted OR - Odds Ratio (tofersen/placebo)		1.46
SE of log(OR)		0.660
95% CI		(0.402, 5.345)
p-value		0.5631
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.073
95% CI		(-0.102, 0.183)
p-value		0.5748

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog/t-cf-fss-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 16JUN2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	6.0	2.1
SE	1.98	1.56
95% CI	(2.07, 9.84)	(-0.99, 5.13)
LS mean difference (tofersen - placebo)		-3.9
SE		2.17
95% CI		(-8.13, 0.37)
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.76, 0.06)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 28		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	12.7	6.9
SE	2.86	2.21
95% CI	(7.07, 18.28)	(2.51, 11.20)
LS mean difference (tofersen - placebo)		-5.8
SE		3.17
95% CI		(-12.03, 0.39)
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.78, 0.09)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	28 (77.8)	50 (69.4)
Number of imputed values per imputation	8 (22.2)	22 (30.6)
LS mean change from baseline	16.0	7.8
SE	3.42	2.73
95% CI	(9.25, 22.67)	(2.40, 13.10)
LS mean difference (tofersen - placebo)		-8.2
SE		3.77
95% CI		(-15.60, -0.82)
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.87, 0.07)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	26 (72.2)	49 (68.1)
Number of imputed values per imputation	10 (27.8)	23 (31.9)
LS mean change from baseline	19.9	9.6
SE	3.29	2.71
95% CI	(13.43, 26.34)	(4.30, 14.93)
LS mean difference (tofersen - placebo)		-10.3
SE		3.60
95% CI		(-17.33, -3.20)
p-value		0.0044
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.93, 0.03)
p-value		0.0685

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 12		
N	36	66
LS mean change from baseline	6.1	2.2
SE	1.91	1.49
95% CI	(2.32, 9.90)	(-0.73, 5.19)
LS mean difference (tofersen - placebo)		-3.9
SE		2.17
95% CI		(-8.18, 0.42)
Week 28		
N	31	61
LS mean change from baseline	12.1	6.0
SE	2.67	1.98
95% CI	(6.84, 17.44)	(2.11, 9.95)
LS mean difference (tofersen - placebo)		-6.1
SE		3.15
95% CI		(-12.36, 0.14)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates better health-related status.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 40		
N	28	50
LS mean change from baseline	15.9	7.7
SE	3.20	2.37
95% CI	(9.55, 22.25)	(3.01, 12.42)
LS mean difference (tofersen - placebo)		-8.2
SE		3.83
95% CI		(-15.80, -0.57)
Week 52		
N	26	49
LS mean change from baseline	19.5	9.1
SE	3.15	2.34
95% CI	(13.27, 25.83)	(4.46, 13.76)
LS mean difference (tofersen - placebo)		-10.4
SE		3.76
95% CI		(-17.94, -2.93)
p-value		0.0071

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates better health-related status.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-aq5-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

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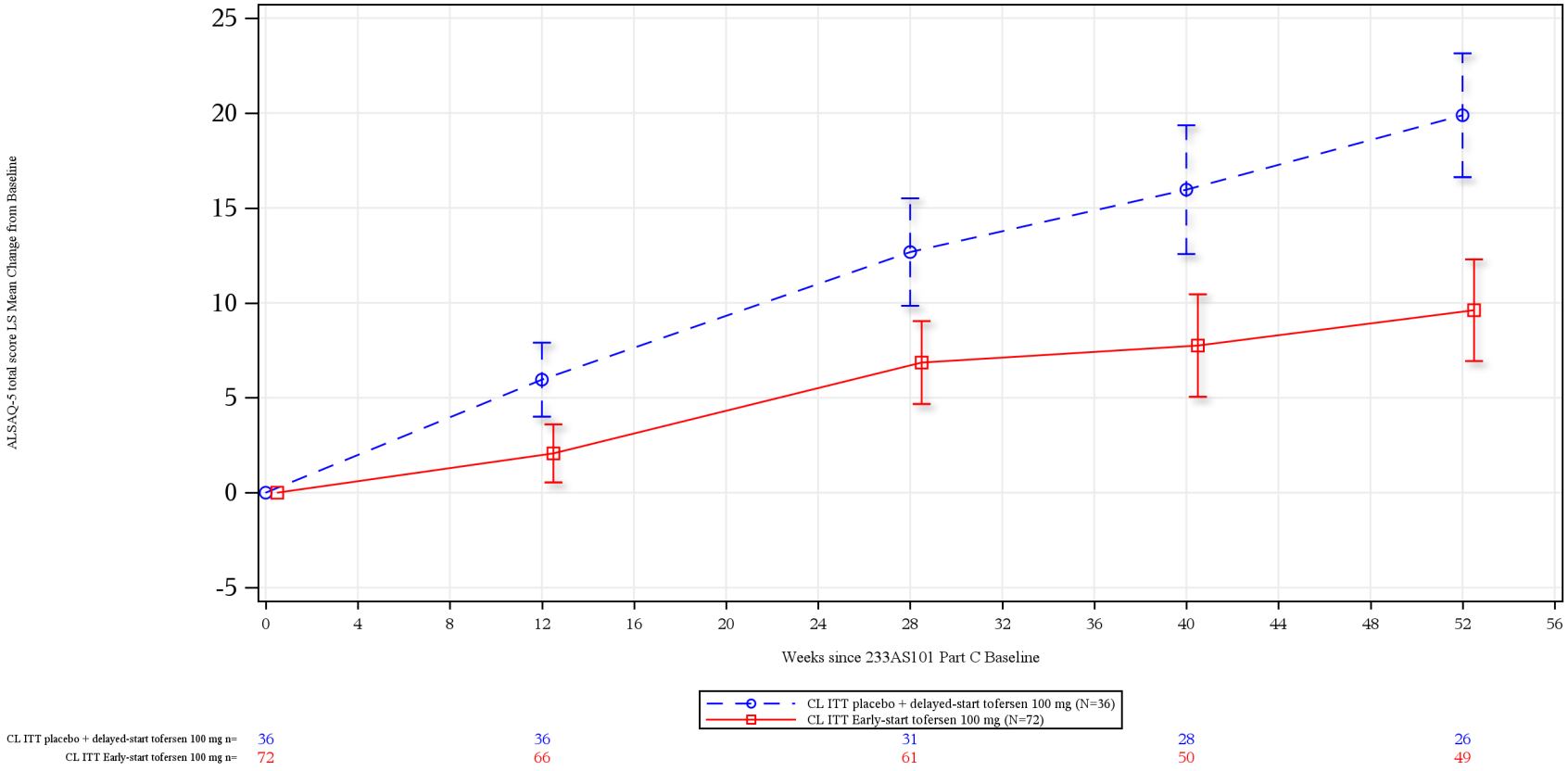

Footnotes are displayed on last page.

Source: biib067/ise/ise-bla2/f-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 23MAR2022

233AS101 and 233AS102 ISE: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla2/f-cf-aq5-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 23MAR2022

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 total score >= 15% at Week 52 using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 total score > = 15%	53.3	32.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.54
SE of log(RR)		0.215
95% CI		(0.355, 0.825)
p-value		0.0043
Adjusted OR - Odds Ratio (tofersen/placebo)		0.20
SE of log(OR)		0.637
95% CI		(0.056, 0.683)
p-value		0.0105
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.21
SE of ARR		0.106
95% CI		(-0.419, -0.002)
p-value		0.0480

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 total score >= 15% at Week 52 using MI for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 total score > = 15%	1.5	7.1
Adjusted RR - Relative Risk (tofersen/placebo)		2.91
SE of log(RR)		1.104
95% CI		(0.334, 25.385)
p-value		0.3329
Adjusted OR - Odds Ratio (tofersen/placebo)		3.11
SE of log(OR)		1.152
95% CI		(0.325, 29.727)
p-value		0.3249
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.044
95% CI		(-0.034, 0.139)
p-value		0.2324

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

Difficult to Stand Up

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	51.9	27.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.51
SE of log(RR)		0.272
95% CI		(0.302, 0.878)
p-value		0.0149
Adjusted OR - Odds Ratio (tofersen/placebo)		0.34
SE of log(OR)		0.464
95% CI		(0.135, 0.834)
p-value		0.0187
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.25
SE of ARR		0.107
95% CI		(-0.457, -0.038)
p-value		0.0207

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 52.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Difficulty Using My Arms and Hands

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	54.2	35.4
Adjusted RR - Relative Risk (tofersen/placebo)		0.61
SE of log(RR)		0.230
95% CI		(0.390, 0.963)
p-value		0.0338
Adjusted OR - Odds Ratio (tofersen/placebo)		0.38
SE of log(OR)		0.478
95% CI		(0.147, 0.958)
p-value		0.0404
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.19
SE of ARR		0.108
95% CI		(-0.399, 0.023)
p-value		0.0815

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 52.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Difficulty Eating Solid Food

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	51.1	41.1
Adjusted RR - Relative Risk (tofersen/placebo)		0.74
SE of log(RR)		0.201
95% CI		(0.499, 1.100)
p-value		0.1366
Adjusted OR - Odds Ratio (tofersen/placebo)		0.48
SE of log(OR)		0.520
95% CI		(0.174, 1.339)
p-value		0.1618
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.108
95% CI		(-0.312, 0.112)
p-value		0.3567

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 52.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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My Speech Not Easy to Understand

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	36.4	41.1
Adjusted RR - Relative Risk (tofersen/placebo)		1.03
SE of log(RR)		0.259
95% CI		(0.622, 1.720)
p-value		0.8954
Adjusted OR - Odds Ratio (tofersen/placebo)		1.07
SE of log(OR)		0.510
95% CI		(0.392, 2.898)
p-value		0.9000
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.106
95% CI		(-0.161, 0.255)
p-value		0.6567

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 52.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

Felt Hopeless About the Future

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in ALSAQ-5 domain score > = 15%	29.3	30.2
Adjusted RR - Relative Risk (tofersen/placebo)		0.94
SE of log(RR)		0.334
95% CI		(0.490, 1.813)
p-value		0.8600
Adjusted OR - Odds Ratio (tofersen/placebo)		0.91
SE of log(OR)		0.534
95% CI		(0.318, 2.581)
p-value		0.8538
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.102
95% CI		(-0.190, 0.209)
p-value		0.9293

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero domain score at baseline are considered as worsening if their domain scores have any increase at Week 52.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Difficult to Stand Up

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	10.8	29.6
Adjusted RR - Relative Risk (tofersen/placebo)		2.81
SE of log(RR)		0.555
95% CI		(0.947, 8.349)
p-value		0.0626
Adjusted OR - Odds Ratio (tofersen/placebo)		3.58
SE of log(OR)		0.642
95% CI		(1.016, 12.589)
p-value		0.0472
ARR - Absolute Risk Reduction (tofersen - placebo)		0.19
SE of ARR		0.080
95% CI		(0.031, 0.344)
p-value		0.0189

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Difficulty Using My Arms and Hands

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	11.7	26.1
Adjusted RR - Relative Risk (tofersen/placebo)		2.43
SE of log(RR)		0.514
95% CI		(0.886, 6.644)
p-value		0.0846
Adjusted OR - Odds Ratio (tofersen/placebo)		3.24
SE of log(OR)		0.648
95% CI		(0.909, 11.538)
p-value		0.0699
ARR - Absolute Risk Reduction (tofersen - placebo)		0.14
SE of ARR		0.079
95% CI		(-0.011, 0.298)
p-value		0.0695

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Difficulty Eating Solid Food

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	3.6	5.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.76
SE of log(RR)		1.100
95% CI		(0.203, 15.207)
p-value		0.6078
Adjusted OR - Odds Ratio (tofersen/placebo)		1.85
SE of log(OR)		1.184
95% CI		(0.181, 18.826)
p-value		0.6042
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.044
95% CI		(-0.070, 0.103)
p-value		0.7089

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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My Speech Not Easy to Understand

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	3.2	0.3
Adjusted RR - Relative Risk (tofersen/placebo)		0.28
SE of log(RR)		1.284
95% CI		(0.023, 3.507)
p-value		0.3258
Adjusted OR - Odds Ratio (tofersen/placebo)		0.27
SE of log(OR)		1.311
95% CI		(0.021, 3.558)
p-value		0.3212
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.03
SE of ARR		0.037
95% CI		(-0.106, 0.038)
p-value		0.3559

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 domain score >= 15% at Week 52 using MI for pooled group CL - ITT population

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Felt Hopeless About the Future

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in ALSAQ-5 domain score > = 15%	20.4	18.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.88
SE of log(RR)		0.435
95% CI		(0.375, 2.062)
p-value		0.7669
Adjusted OR - Odds Ratio (tofersen/placebo)		0.85
SE of log(OR)		0.539
95% CI		(0.296, 2.450)
p-value		0.7666
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.02
SE of ARR		0.084
95% CI		(-0.184, 0.146)
p-value		0.8173

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog/t-cf-aq5-d-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 06JUL2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-3.6	1.2
SE	1.62	1.30
95% CI	(-6.73, -0.39)	(-1.36, 3.72)
LS mean difference (tofersen - placebo)		4.7
SE		1.79
95% CI		(1.24, 8.25)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(0.02, 0.84)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Week 24		
Number of observations per imputation	32 (88.9)	63 (87.5)
Number of imputed values per imputation	4 (11.1)	9 (12.5)
LS mean change from baseline	-5.4	0.2
SE	1.83	1.42
95% CI	(-8.98, -1.81)	(-2.59, 2.96)
LS mean difference (tofersen - placebo)		5.6
SE		2.03
95% CI		(1.60, 9.56)
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(0.04, 0.90)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Week 48		
Number of observations per imputation	27 (75.0)	50 (69.4)
Number of imputed values per imputation	9 (25.0)	22 (30.6)
LS mean change from baseline	-2.2	-0.3
SE	1.95	1.56
95% CI	(-6.05, 1.58)	(-3.39, 2.72)
LS mean difference (tofersen - placebo)		1.9
SE		2.15
95% CI		(-2.32, 6.12)
p-value		0.3774
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.34, 0.59)
p-value		0.6043

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

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Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-2.6	-3.1
SE	1.10	0.87
95% CI	(-4.72, -0.42)	(-4.82, -1.40)
LS mean difference (tofersen - placebo)		-0.5
SE		1.21
95% CI		(-2.90, 1.82)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.49, 0.32)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Week 24		
Number of observations per imputation	32 (88.9)	63 (87.5)
Number of imputed values per imputation	4 (11.1)	9 (12.5)
LS mean change from baseline	-3.7	-3.6
SE	1.25	0.96
95% CI	(-6.17, -1.29)	(-5.47, -1.69)
LS mean difference (tofersen - placebo)		0.2
SE		1.38
95% CI		(-2.55, 2.85)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.37, 0.48)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	**Early-start tofersen 100 mg**
	(N=36)	**(N=72)**
Week 48		
Number of observations per imputation	27 (75.0)	50 (69.4)
Number of imputed values per imputation	9 (25.0)	22 (30.6)
LS mean change from baseline	-7.0	-3.8
SE	1.37	1.10
95% CI	(-9.66, -4.30)	(-5.98, -1.67)
LS mean difference (tofersen - placebo)		3.2
SE		1.51
95% CI		(0.19, 6.11)
p-value		0.0369
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.02, 0.93)
p-value		0.0597

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point MMRM analysis for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-3.1	1.6
SE	1.57	1.24
95% CI	(-6.22, 0.01)	(-0.83, 4.08)
LS mean difference (tofersen - placebo)		4.7
SE		1.78
95% CI		(1.20, 8.25)
Week 24		
N	32	63
LS mean change from baseline	-5.0	0.6
SE	1.74	1.33
95% CI	(-8.42, -1.51)	(-2.03, 3.23)
LS mean difference (tofersen - placebo)		5.6
SE		2.00
95% CI		(1.59, 9.53)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point MMRM analysis for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 48		
N	27	50
LS mean change from baseline	-2.6	-0.5
SE	1.86	1.42
95% CI	(-6.26, 1.15)	(-3.36, 2.29)
LS mean difference (tofersen - placebo)		2.0
SE		2.15
95% CI		(-2.26, 6.32)
p-value		0.3495

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point MMRM analysis for pooled group CL - ITT population

Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	36	66
LS mean change from baseline	-2.6	-3.1
SE	1.08	0.85
95% CI	(-4.72, -0.44)	(-4.79, -1.41)
LS mean difference (tofersen - placebo)		-0.5
SE		1.20
95% CI		(-2.89, 1.86)
Week 24		
N	32	63
LS mean change from baseline	-3.8	-3.7
SE	1.20	0.92
95% CI	(-6.21, -1.43)	(-5.51, -1.86)
LS mean difference (tofersen - placebo)		0.1
SE		1.36
95% CI		(-2.57, 2.85)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: SF-36 component summary change from baseline by time point MMRM analysis for pooled group CL - ITT population

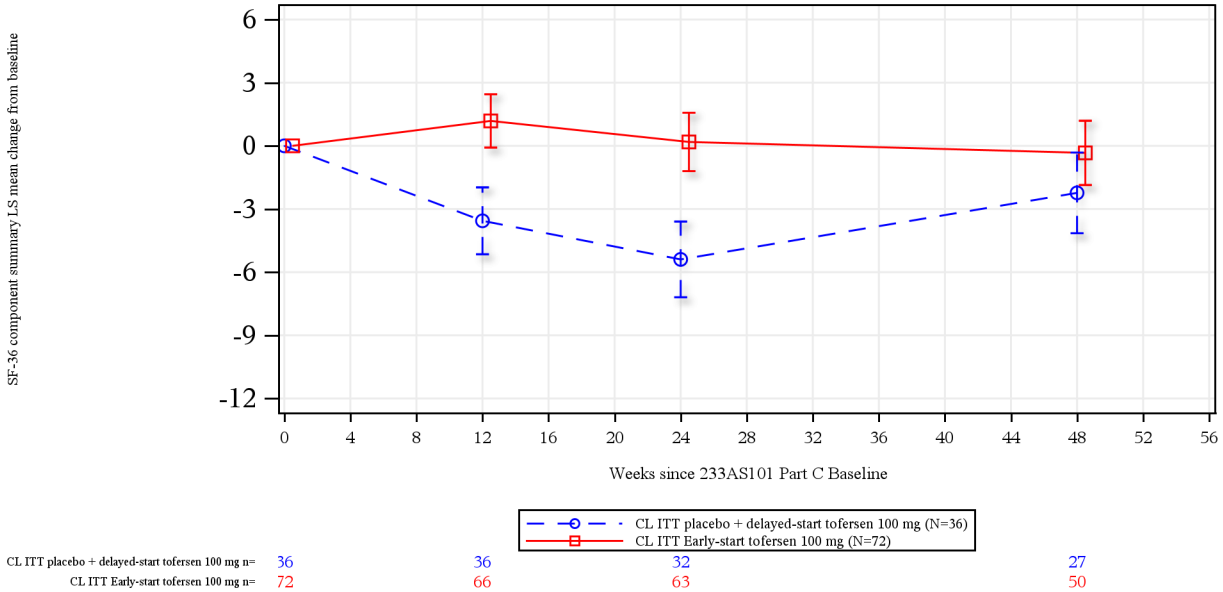
Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 48		
N	27	50
LS mean change from baseline	-6.8	-3.5
SE	1.30	1.00
95% CI	(-9.33, -4.17)	(-5.49, -1.53)
LS mean difference (tofersen - placebo)		3.2
SE		1.49
95% CI		(0.27, 6.22)
p-value		0.0330

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A positive change indicates an improvement in health state.
NOTE 3: Missing values in particular visits up to and including Week 52 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; MMRM = mixed model for repeated measures; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-sf36-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Line plot of SF-36 component summary change LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

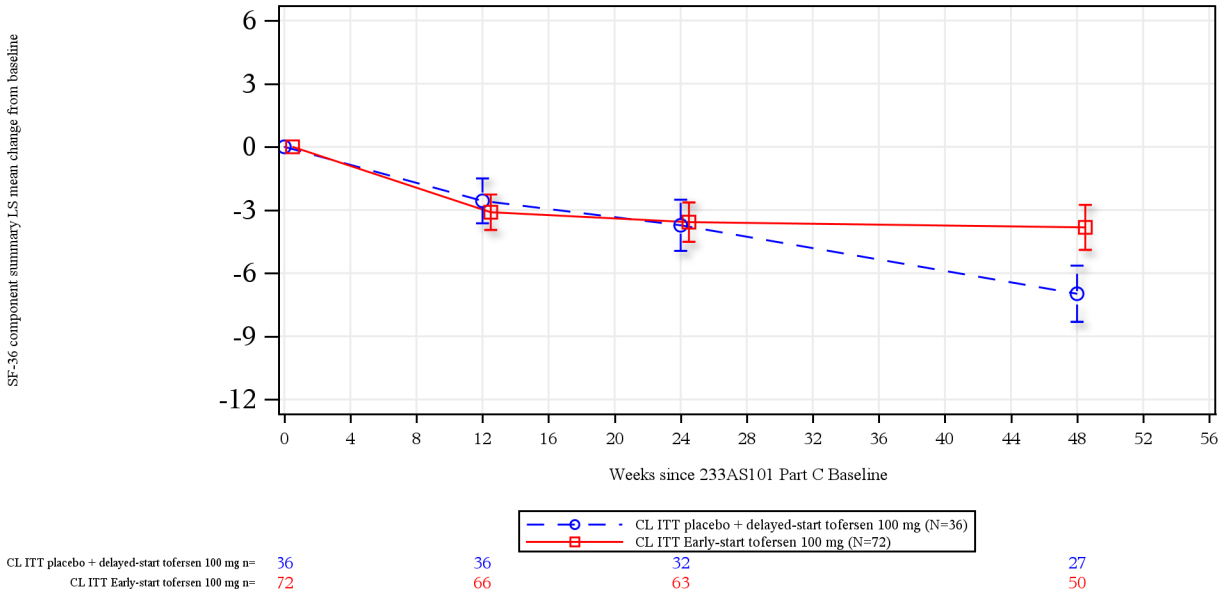
Mental Component Summary



NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla2/f-cf-sf36-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31MAR2022

233AS101 and 233AS102 ISE: Line plot of SF-36 component summary change LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

Physical Component Summary



NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A positive change indicates an improvement in health state.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline SF-36 component summary, and use of riluzole or edaravone.
Abbreviations: SF-36 = 36 Item Short Form Health Survey; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla2/f-cf-sf36-anc-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 31MAR2022

233AS101 and 233AS102 ISE: Summary of proportion of worsening in SF-36 component summary at Week 48 using MI for pooled group CL - ITT population

Page: 1 of 2

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in SF-36 MCS >= 9.6	24.8	14.8
Adjusted RR - Relative Risk (tofersen/placebo)		0.56
SE of log(RR)		0.466
95% CI		(0.226, 1.408)
p-value		0.2195
Adjusted OR - Odds Ratio (tofersen/placebo)		0.48
SE of log(OR)		0.598
95% CI		(0.149, 1.558)
p-value		0.2228
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.10
SE of ARR		0.093
95% CI		(-0.281, 0.082)
p-value		0.2826

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in SF-36 component summary at Week 48 using MI for pooled group CL - ITT population

Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in SF-36 PCS >= 9.4	38.5	21.5
Adjusted RR - Relative Risk (tofersen/placebo)		0.53
SE of log(RR)		0.348
95% CI		(0.267, 1.043)
p-value		0.0657
Adjusted OR - Odds Ratio (tofersen/placebo)		0.39
SE of log(OR)		0.514
95% CI		(0.143, 1.073)
p-value		0.0682
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.17
SE of ARR		0.103
95% CI		(-0.373, 0.033)
p-value		0.0999

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in SF-36 component summary at Week 48 using MI for pooled group CL - ITT population

Mental Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in SF-36 MCS >= 9.6	15.2	16.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.00
SE of log(RR)		0.501
95% CI		(0.375, 2.679)
p-value		0.9962
Adjusted OR - Odds Ratio (tofersen/placebo)		1.00
SE of log(OR)		0.599
95% CI		(0.310, 3.249)
p-value		0.9951
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.077
95% CI		(-0.143, 0.160)
p-value		0.9140

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in SF-36 component summary at Week 48 using MI for pooled group CL - ITT population

Physical Component Summary

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in SF-36 PCS >= 9.4	1.3	4.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.71
SE of log(RR)		1.152
95% CI		(0.178, 16.323)
p-value		0.6430
Adjusted OR - Odds Ratio (tofersen/placebo)		1.74
SE of log(OR)		1.200
95% CI		(0.166, 18.342)
p-value		0.6428
ARR - Absolute Risk Reduction (tofersen - placebo)		0.03
SE of ARR		0.038
95% CI		(-0.049, 0.101)
p-value		0.4936

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SF-36 = 36 Item Short Form Health Survey.
Source: biib067/valueaccess/amnog/t-cf-sf36-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: WPAI-Q6 change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
Week 12		
Number of observations per imputation	35 (97.2)	66 (91.7)
Number of imputed values per imputation	1 (2.8)	6 (8.3)
LS mean change from baseline	0.5	0.6
SE	0.37	0.29
95% CI	(-0.21, 1.23)	(0.02, 1.16)
LS mean difference (tofersen - placebo)		0.1
SE		0.40
95% CI		(-0.71, 0.87)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.44, 0.38)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-wpai-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 28JUN2023

233AS101 and 233AS102 ISE: WPAI-Q6 change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 24		
Number of observations per imputation	33 (91.7)	64 (88.9)
Number of imputed values per imputation	3 (8.3)	8 (11.1)
LS mean change from baseline	0.9	0.5
SE	0.43	0.34
95% CI	(0.04, 1.72)	(-0.13, 1.19)
LS mean difference (tofersen - placebo)		-0.4
SE		0.47
95% CI		(-1.28, 0.57)
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.65, 0.19)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-wpai-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 28JUN2023

233AS101 and 233AS102 ISE: WPAI-Q6 change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 48		
Number of observations per imputation	26 (72.2)	48 (66.7)
Number of imputed values per imputation	10 (27.8)	24 (33.3)
LS mean change from baseline	2.1	1.3
SE	0.41	0.32
95% CI	(1.33, 2.93)	(0.67, 1.94)
LS mean difference (tofersen - placebo)		-0.8
SE		0.44
95% CI		(-1.69, 0.03)
p-value		0.0573
Hedge's g standardized mean difference (tofersen - placebo)		-0.5
95% CI		(-0.97, 0.00)
p-value		0.0491

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-wpai-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 28JUN2023

233AS101 and 233AS102 ISE: WPAI-Q6 change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 12		
N	35	66
LS mean change from baseline	0.5	0.6
SE	0.35	0.28
95% CI	(-0.21, 1.20)	(0.05, 1.15)
LS mean difference (tofersen - placebo)		0.1
SE		0.40
95% CI		(-0.69, 0.90)
Week 24		
N	33	64
LS mean change from baseline	1.0	0.7
SE	0.41	0.31
95% CI	(0.22, 1.86)	(0.07, 1.32)
LS mean difference (tofersen - placebo)		-0.3
SE		0.48
95% CI		(-1.30, 0.61)

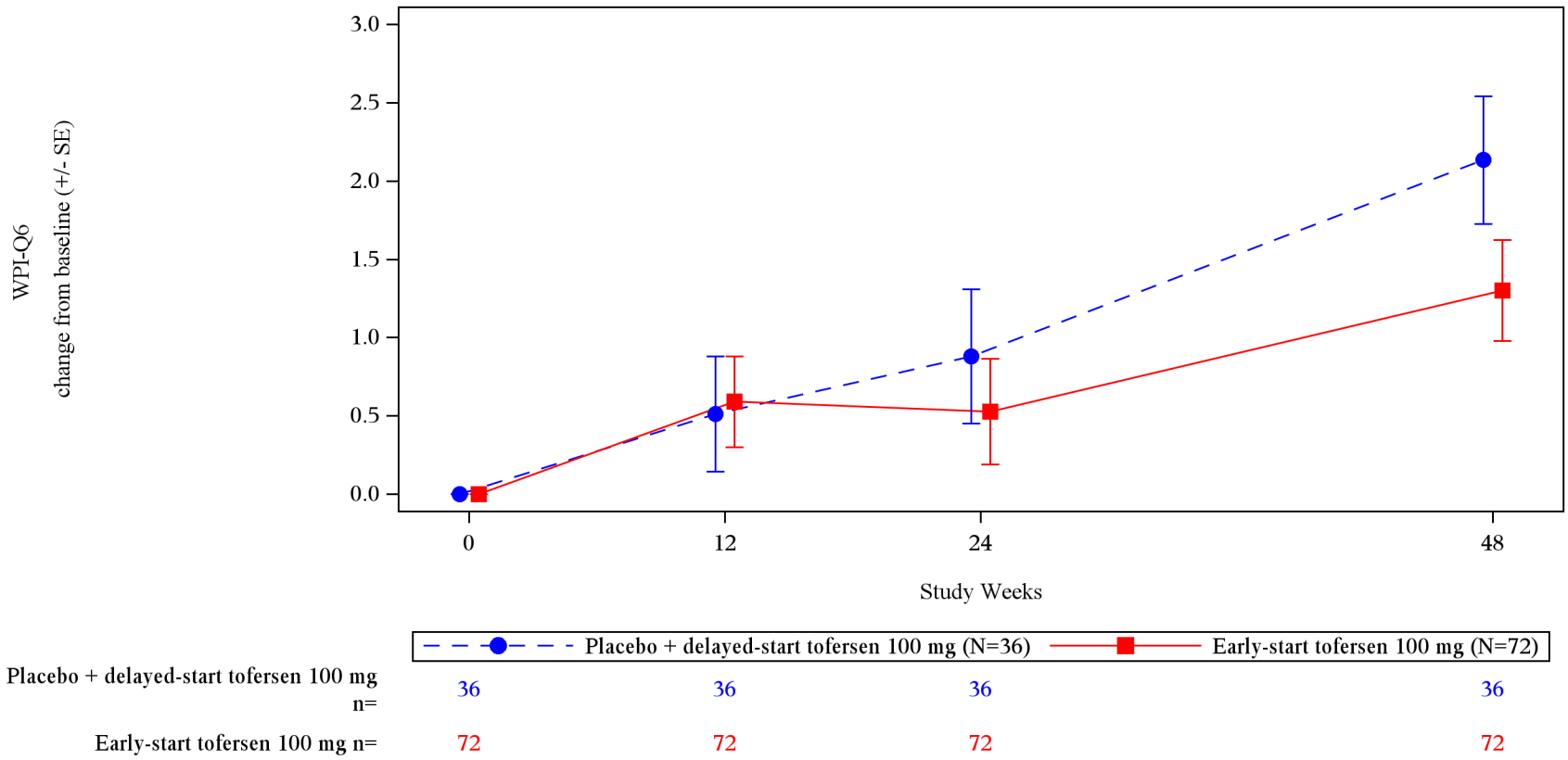
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less activity impairment.
NOTE 3: Missing values in particular visits up to and including Week 48 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-wpai-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: WPAI-Q6 change from baseline by time point MMRM analysis for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 48		
N	26	48
LS mean change from baseline	2.1	1.2
SE	0.41	0.32
95% CI	(1.29, 2.92)	(0.56, 1.81)
LS mean difference (tofersen - placebo)		-0.9
SE		0.47
95% CI		(-1.87, 0.02)
p-value		0.0560

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: A negative change indicates less activity impairment.
NOTE 3: Missing values in particular visits up to and including Week 48 are imputed by MMRM model using an unstructured (UN) variance-covariance matrix structure. Treatment group, visit, treatment-by-visit interaction, baseline score and baseline score-by-visit interaction, baseline plasma NfL and baseline-plasma-NfL-by-visit interaction, and use of riluzole or edaravone terms are included in the model. Nominal p-value is presented.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/t-cf-wpai-mmrm-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 30JUN2023

233AS101 and 233AS102 ISE: Line plot of WPI-Q6 LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population



Footnotes are displayed on last page.

Source: biib067/valueaccess/amnog/f-cf-wpai-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: Line plot of WPI-Q6 LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug and presented as Day 1. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less activity impairment.
NOTE 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline WPAI-Q6, and use of riluzole or edaravone.
Abbreviations: WPAI = Work Productivity and Activity Inventory; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog/f-cf-wpai-ancmi-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 29JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of worsening in WPAI-Q6 >= 15% at Week 48 using MI for pooled group CL - ITT population

Page: 1 of 1

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with worsening in WPAI-Q6 score > = 15%	64.0	33.7
Adjusted RR - Relative Risk (tofersen/placebo)		0.52
SE of log(RR)		0.237
95% CI		(0.329, 0.833)
p-value		0.0063
Adjusted OR - Odds Ratio (tofersen/placebo)		0.29
SE of log(OR)		0.472
95% CI		(0.114, 0.724)
p-value		0.0082
ARR - Absolute Risk Reduction (tofersen - placebo)		-0.30
SE of ARR		0.107
95% CI		(-0.512, -0.094)
p-value		0.0045

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero WPAI scores at baseline are considered as worsening if their WPAI scores have any increase at Week 28.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propw-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in WPAI-Q6 >= 15% at Week 48 using MI for pooled group CL - ITT population

Page: 1 of 1

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Average proportion of subjects with improvement in WPAI-Q6 score > = 15%	4.5	13.7
Adjusted RR - Relative Risk (tofersen/placebo)		3.32
SE of log(RR)		1.067
95% CI		(0.409, 26.892)
p-value		0.2614
Adjusted OR - Odds Ratio (tofersen/placebo)		3.53
SE of log(OR)		1.072
95% CI		(0.431, 28.827)
p-value		0.2398
ARR - Absolute Risk Reduction (tofersen - placebo)		0.09
SE of ARR		0.061
95% CI		(-0.027, 0.213)
p-value		0.1292

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
NOTE 4: The subjects with zero WPAI scores at baseline are considered as worsening if their WPAI scores have any increase at Week 28.
Abbreviations: WPAI = Work Productivity and Activity Inventor.
Source: biib067/valueaccess/amnog/t-cf-wpa-propim-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 05JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

Suicidal Ideation (1-5)

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	3 (8.3)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.677
95% CI		(0.265, 3.769)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.739
95% CI		(0.235, 4.253)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.056
95% CI		(-0.111, 0.111)
p-value		1.0000

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(1) Wish to be dead

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	2 (5.6)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.811
95% CI		(0.255, 6.131)
p-value		0.7833
OR - Odds Ratio (tofersen/placebo)		1.27
SE of log (OR)		0.863
95% CI		(0.234, 6.882)
p-value		0.7827
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.049
95% CI		(-0.081, 0.109)
p-value		0.7747

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

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(2) Non-specific active suicidal thoughts

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	2 (5.6)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.979
95% CI		(0.073, 3.406)
p-value		0.4789
OR - Odds Ratio (tofersen/placebo)		0.49
SE of log (OR)		1.022
95% CI		(0.066, 3.597)
p-value		0.4797
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.043
95% CI		(-0.112, 0.056)
p-value		0.5164

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(3) Active suicidal ideation with any methods (not plan) without intent to act

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	[redacted]	
RR - Relative Risk (tofersen/placebo)		1.52
SE of log (RR)		1.620
95% CI		(0.063, 36.421)
p-value		0.7959
OR - Odds Ratio (tofersen/placebo)		1.53
SE of log (OR)		1.646
95% CI		(0.061, 38.535)
p-value		0.7956
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.025
95% CI		(-0.042, 0.056)
p-value		0.7803

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(4) Active suicidal ideation with some intent to act, without specific plan

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(5) Active suicidal ideation with specific plan and intent

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

Suicidal Behavior (6-11)

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(6) Preparatory acts or behavior

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(7) Aborted attempt

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(8) Interrupted attempt

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(9) Actual attempt

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(10) Suicidal behavior

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

(11) Suicide

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISS: Summary of C-SSRS suicidal ideation or suicidal behavior at any post-baseline visit up to Week 52 using last observation carried over (LOCF) for pooled group CL - ITT population

Self-injurious behavior without suicidal intent

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with answer = YES	0	0

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: For any missing in questions 1-11 and 'self-injurious behavior without suicidal intent', the last non-missing observation is carried over for summary.
NOTE 3: For suicidal ideation (1-5) or suicidal behavior (6-11), the subject is considered with answer = Yes if the subject answered Yes to any suicidal ideation questions or any suicidal behavior questions at any post-baseline visits up to Week 52.
Abbreviations: C-SSRS = Columbia Suicide Severity Rating scale.
Source: biib067/valueaccess/amnog/t-cssrs-prop-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 07JUL2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 12 , Pre-dose		
n	33	64
LS mean change from baseline	0.1	0.1
SE	0.19	0.14
95% CI	(-0.23, 0.52)	(-0.17, 0.39)
LS mean difference (tofersen - placebo)		0.0
SE		0.20
95% CI		(-0.43, 0.36)
p-value		0.8650
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.47, 0.37)
p-value		0.8247

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 12 , Post-dose		
n	35	62
LS mean change from baseline	0.4	0.1
SE	0.20	0.15
95% CI	(-0.02, 0.76)	(-0.21, 0.40)
LS mean difference (tofersen - placebo)		-0.3
SE		0.21
95% CI		(-0.70, 0.14)
p-value		0.1896
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.70, 0.13)
p-value		0.1824

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
n	30	58
LS mean change from baseline	0.1	0.1
SE	0.24	0.19
95% CI	(-0.42, 0.54)	(-0.23, 0.51)
LS mean difference (tofersen - placebo)		0.1
SE		0.27
95% CI		(-0.46, 0.63)
p-value		0.7517
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.43, 0.45)
p-value		0.9601

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40 , Pre-dose		
n	27	49
LS mean change from baseline	-0.3	0.0
SE	0.31	0.24
95% CI	(-0.91, 0.31)	(-0.48, 0.46)
LS mean difference (tofersen - placebo)		0.3
SE		0.33
95% CI		(-0.38, 0.95)
p-value		0.3923
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.37, 0.57)
p-value		0.6851

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40 , Post-dose		
n	25	46
LS mean change from baseline	-0.1	0.2
SE	0.26	0.20
95% CI	(-0.64, 0.41)	(-0.18, 0.62)
LS mean difference (tofersen - placebo)		0.3
SE		0.29
95% CI		(-0.24, 0.91)
p-value		0.2515
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.39, 0.59)
p-value		0.6877

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 52 , Pre-dose		
n	22	46
LS mean change from baseline	-0.5	0.2
SE	0.29	0.23
95% CI	(-1.11, 0.06)	(-0.30, 0.61)
LS mean difference (tofersen - placebo)		0.7
SE		0.33
95% CI		(0.03, 1.34)
p-value		0.0415
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.18, 0.84)
p-value		0.2009

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISE: MMSE total score change from baseline by visit ANCOVA analysis (observed data) for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52 , Post-dose		
n	22	42
LS mean change from baseline	-0.4	0.0
SE	0.28	0.22
95% CI	(-0.95, 0.19)	(-0.41, 0.47)
LS mean difference (tofersen - placebo)		0.4
SE		0.32
95% CI		(-0.23, 1.05)
p-value		0.2026
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.40, 0.64)
p-value		0.6462

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: When there are multiple assessments during a single visit, the minimal value is taken as the value for that visit.
NOTE 3: ANCOVA model includes treatment as a fixed effect and adjusting for the following covariates: baseline plasma NfL, baseline MMSE total score, and use of riluzole or edaravone.
Abbreviations: MMSE = Mini-Mental State Examination; ANCOVA = analysis of covariance; LS = least square.
Source: biib067/valueaccess/amnog/t-mmse-chg-byvis-clitt.sas **Data Cutoff:** 16JAN2022 **Run Date:** 01AUG2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	35 (97.2)	71 (98.6)
RR - Relative Risk (tofersen/placebo)		1.01
SE of log (RR)		0.031
95% CI		(0.954, 1.079)
p-value		0.6520
OR - Odds Ratio (tofersen/placebo)		2.03
SE of log (OR)		1.429
95% CI		(0.123, 33.400)
p-value		0.6207
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.031
95% CI		(-0.046, 0.074)
p-value		0.6506

Source: biib067/valueaccess/amnog/t-ae-event-clitt.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Nervous system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	31 (86.1)	57 (79.2)
RR - Relative Risk (tofersen/placebo)		0.92
SE of log (RR)		0.090
95% CI		(0.770, 1.097)
p-value		0.3512
OR - Odds Ratio (tofersen/placebo)		0.61
SE of log (OR)		0.563
95% CI		(0.203, 1.846)
p-value		0.3842
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.075
95% CI		(-0.216, 0.077)
p-value		0.3540

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Injury, poisoning and procedural complications

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	33 (91.7)	56 (77.8)
RR - Relative Risk (tofersen/placebo)		0.85
SE of log (RR)		0.081
95% CI		(0.725, 0.994)
p-value		0.0415
OR - Odds Ratio (tofersen/placebo)		0.32
SE of log (OR)		0.666
95% CI		(0.086, 1.175)
p-value		0.0857
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.14
SE of ARR		0.067
95% CI		(-0.271, -0.007)
p-value		0.0389

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Musculoskeletal and connective tissue disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	26 (72.2)	56 (77.8)
RR - Relative Risk (tofersen/placebo)		1.08
SE of log (RR)		0.121
95% CI		(0.849, 1.365)
p-value		0.5404
OR - Odds Ratio (tofersen/placebo)		1.35
SE of log (OR)		0.468
95% CI		(0.538, 3.367)
p-value		0.5251
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.089
95% CI		(-0.119, 0.231)
p-value		0.5338

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

Gastrointestinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	27 (75.0)	45 (62.5)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.133
95% CI		(0.643, 1.081)
p-value		0.1693
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.455
95% CI		(0.228, 1.356)
p-value		0.1968
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.092
95% CI		(-0.305, 0.055)
p-value		0.1742

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Infections and infestations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	27 (75.0)	43 (59.7)
RR - Relative Risk (tofersen/placebo)		0.80
SE of log (RR)		0.136
95% CI		(0.609, 1.041)
p-value		0.0951
OR - Odds Ratio (tofersen/placebo)		0.49
SE of log (OR)		0.454
95% CI		(0.203, 1.203)
p-value		0.1204
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.15
SE of ARR		0.092
95% CI		(-0.334, 0.028)
p-value		0.0985

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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General disorders and administration site conditions

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	22 (61.1)	40 (55.6)
RR - Relative Risk (tofersen/placebo)		0.91
SE of log (RR)		0.170
95% CI		(0.652, 1.268)
p-value		0.5743
OR - Odds Ratio (tofersen/placebo)		0.80
SE of log (OR)		0.416
95% CI		(0.352, 1.798)
p-value		0.5823
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.100
95% CI		(-0.252, 0.141)
p-value		0.5791

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Investigations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	13 (36.1)	38 (52.8)
RR - Relative Risk (tofersen/placebo)		1.46
SE of log (RR)		0.248
95% CI		(0.899, 2.377)
p-value		0.1262
OR - Odds Ratio (tofersen/placebo)		1.98
SE of log (OR)		0.420
95% CI		(0.869, 4.501)
p-value		0.1043
ARR - Absolute Risk Reduction (tofersen/placebo)		0.17
SE of ARR		0.099
95% CI		(-0.028, 0.361)
p-value		0.0934

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	19 (52.8)	36 (50.0)
RR - Relative Risk (tofersen/placebo)		0.95
SE of log (RR)		0.197
95% CI		(0.644, 1.393)
p-value		0.7836
OR - Odds Ratio (tofersen/placebo)		0.89
SE of log (OR)		0.409
95% CI		(0.402, 1.993)
p-value		0.7855
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.102
95% CI		(-0.228, 0.172)
p-value		0.7853

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Skin and subcutaneous tissue disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	23 (31.9)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.305
95% CI		(0.576, 1.899)
p-value		0.8839
OR - Odds Ratio (tofersen/placebo)		1.07
SE of log (OR)		0.441
95% CI		(0.449, 2.534)
p-value		0.8835
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.094
95% CI		(-0.171, 0.199)
p-value		0.8830

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Psychiatric disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	21 (29.2)
RR - Relative Risk (tofersen/placebo)		0.95
SE of log (RR)		0.311
95% CI		(0.519, 1.757)
p-value		0.8812
OR - Odds Ratio (tofersen/placebo)		0.94
SE of log (OR)		0.445
95% CI		(0.391, 2.239)
p-value		0.8816
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.094
95% CI		(-0.197, 0.170)
p-value		0.8821

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Renal and urinary disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.474
95% CI		(0.592, 3.801)
p-value		0.3927
OR - Odds Ratio (tofersen/placebo)		1.63
SE of log (OR)		0.563
95% CI		(0.542, 4.914)
p-value		0.3842
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.075
95% CI		(-0.077, 0.216)
p-value		0.3540

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Metabolism and nutrition disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	12 (33.3)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.354
95% CI		(0.250, 1.000)
p-value		0.0499
OR - Odds Ratio (tofersen/placebo)		0.40
SE of log (OR)		0.474
95% CI		(0.158, 1.013)
p-value		0.0534
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.17
SE of ARR		0.090
95% CI		(-0.343, 0.010)
p-value		0.0641

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Eye disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.64
SE of log (RR)		0.461
95% CI		(0.261, 1.586)
p-value		0.3376
OR - Odds Ratio (tofersen/placebo)		0.59
SE of log (OR)		0.552
95% CI		(0.201, 1.745)
p-value		0.3417
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.077
95% CI		(-0.220, 0.081)
p-value		0.3647

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Cardiac disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.60
SE of log (RR)		0.570
95% CI		(0.196, 1.834)
p-value		0.3702
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.643
95% CI		(0.160, 1.989)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.066
95% CI		(-0.185, 0.074)
p-value		0.4014

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Immune system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.612
95% CI		(0.226, 2.491)
p-value		0.6385
OR - Odds Ratio (tofersen/placebo)		0.73
SE of log (OR)		0.680
95% CI		(0.192, 2.760)
p-value		0.6398
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.062
95% CI		(-0.149, 0.093)
p-value		0.6525

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Vascular disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.60
SE of log (RR)		0.570
95% CI		(0.196, 1.834)
p-value		0.3702
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.643
95% CI		(0.160, 1.989)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.066
95% CI		(-0.185, 0.074)
p-value		0.4014

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Nervous system disorders/Headache

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	22 (61.1)	46 (63.9)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.160
95% CI		(0.764, 1.430)
p-value		0.7808
OR - Odds Ratio (tofersen/placebo)		1.13
SE of log (OR)		0.421
95% CI		(0.494, 2.569)
p-value		0.7781
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.099
95% CI		(-0.166, 0.222)
p-value		0.7791

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Procedural pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	26 (72.2)	45 (62.5)
RR - Relative Risk (tofersen/placebo)		0.87
SE of log (RR)		0.138
95% CI		(0.660, 1.134)
p-value		0.2944
OR - Odds Ratio (tofersen/placebo)		0.64
SE of log (OR)		0.445
95% CI		(0.268, 1.532)
p-value		0.3173
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.094
95% CI		(-0.281, 0.087)
p-value		0.3008

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Musculoskeletal and connective tissue disorders/Back pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	10 (27.8)	31 (43.1)
RR - Relative Risk (tofersen/placebo)		1.55
SE of log (RR)		0.301
95% CI		(0.859, 2.796)
p-value		0.1454
OR - Odds Ratio (tofersen/placebo)		1.97
SE of log (OR)		0.442
95% CI		(0.827, 4.672)
p-value		0.1260
ARR - Absolute Risk Reduction (tofersen/placebo)		0.15
SE of ARR		0.095
95% CI		(-0.033, 0.338)
p-value		0.1069

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Pain in extremity

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	14 (38.9)	28 (38.9)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.256
95% CI		(0.606, 1.651)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.419
95% CI		(0.440, 2.272)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.100
95% CI		(-0.195, 0.195)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Fall

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	24 (66.7)	25 (34.7)
RR - Relative Risk (tofersen/placebo)		0.52
SE of log (RR)		0.200
95% CI		(0.352, 0.771)
p-value		0.0011
OR - Odds Ratio (tofersen/placebo)		0.27
SE of log (OR)		0.432
95% CI		(0.114, 0.620)
p-value		0.0022
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.32
SE of ARR		0.097
95% CI		(-0.509, -0.130)
p-value		0.0009

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Arthralgia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	10 (27.8)	23 (31.9)
RR - Relative Risk (tofersen/placebo)		1.15
SE of log (RR)		0.319
95% CI		(0.615, 2.149)
p-value		0.6614
OR - Odds Ratio (tofersen/placebo)		1.22
SE of log (OR)		0.450
95% CI		(0.505, 2.947)
p-value		0.6579
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.093
95% CI		(-0.140, 0.223)
p-value		0.6531

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Investigations/CSF protein increased

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	20 (27.8)
RR - Relative Risk (tofersen/placebo)		1.67
SE of log (RR)		0.418
95% CI		(0.734, 3.784)
p-value		0.2220
OR - Odds Ratio (tofersen/placebo)		1.92
SE of log (OR)		0.519
95% CI		(0.696, 5.317)
p-value		0.2076
ARR - Absolute Risk Reduction (tofersen/placebo)		0.11
SE of ARR		0.082
95% CI		(-0.049, 0.271)
p-value		0.1728

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Fatigue

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	10 (27.8)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		0.90
SE of log (RR)		0.337
95% CI		(0.464, 1.744)
p-value		0.7549
OR - Odds Ratio (tofersen/placebo)		0.87
SE of log (OR)		0.461
95% CI		(0.351, 2.139)
p-value		0.7563
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.090
95% CI		(-0.205, 0.149)
p-value		0.7587

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/COVID-19

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.425
95% CI		(0.652, 3.450)
p-value		0.3400
OR - Odds Ratio (tofersen/placebo)		1.67
SE of log (OR)		0.524
95% CI		(0.597, 4.650)
p-value		0.3292
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.080
95% CI		(-0.074, 0.241)
p-value		0.2999

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Investigations/CSF white blood cell count increased

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		4.50
SE of log (RR)		0.717
95% CI		(1.104, 18.340)
p-value		0.0359
OR - Odds Ratio (tofersen/placebo)		5.67
SE of log (OR)		0.777
95% CI		(1.236, 25.976)
p-value		0.0256
ARR - Absolute Risk Reduction (tofersen/placebo)		0.19
SE of ARR		0.064
95% CI		(0.070, 0.319)
p-value		0.0023

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Myalgia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		2.25
SE of log (RR)		0.514
95% CI		(0.822, 6.158)
p-value		0.1144
OR - Odds Ratio (tofersen/placebo)		2.67
SE of log (OR)		0.596
95% CI		(0.829, 8.578)
p-value		0.0999
ARR - Absolute Risk Reduction (tofersen/placebo)		0.14
SE of ARR		0.073
95% CI		(-0.004, 0.282)
p-value		0.0575

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post lumbar puncture syndrome

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	15 (41.7)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		0.57
SE of log (RR)		0.290
95% CI		(0.321, 0.999)
p-value		0.0498
OR - Odds Ratio (tofersen/placebo)		0.43
SE of log (OR)		0.437
95% CI		(0.184, 1.020)
p-value		0.0555
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.18
SE of ARR		0.096
95% CI		(-0.369, 0.008)
p-value		0.0606

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Nausea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	16 (22.2)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.382
95% CI		(0.473, 2.114)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.491
95% CI		(0.382, 2.618)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.085
95% CI		(-0.166, 0.166)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Muscle spasms

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	14 (19.4)
RR - Relative Risk (tofersen/placebo)		1.17
SE of log (RR)		0.443
95% CI		(0.489, 2.781)
p-value		0.7280
OR - Odds Ratio (tofersen/placebo)		1.21
SE of log (OR)		0.537
95% CI		(0.421, 3.459)
p-value		0.7263
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.078
95% CI		(-0.124, 0.180)
p-value		0.7206

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Constipation

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.59
SE of log (RR)		0.355
95% CI		(0.295, 1.185)
p-value		0.1386
OR - Odds Ratio (tofersen/placebo)		0.50
SE of log (OR)		0.474
95% CI		(0.198, 1.268)
p-value		0.1446
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.13
SE of ARR		0.089
95% CI		(-0.300, 0.050)
p-value		0.1609

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.81
SE of log (RR)		0.400
95% CI		(0.371, 1.781)
p-value		0.6040
OR - Odds Ratio (tofersen/placebo)		0.77
SE of log (OR)		0.505
95% CI		(0.287, 2.073)
p-value		0.6066
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.083
95% CI		(-0.204, 0.121)
p-value		0.6148

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Salivary hypersecretion

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		3.00
SE of log (RR)		0.736
95% CI		(0.709, 12.694)
p-value		0.1355
OR - Odds Ratio (tofersen/placebo)		3.40
SE of log (OR)		0.793
95% CI		(0.718, 16.098)
p-value		0.1229
ARR - Absolute Risk Reduction (tofersen/placebo)		0.11
SE of ARR		0.058
95% CI		(-0.003, 0.225)
p-value		0.0562

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Dizziness

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	11 (15.3)
RR - Relative Risk (tofersen/placebo)		0.69
SE of log (RR)		0.417
95% CI		(0.303, 1.558)
p-value		0.3694
OR - Odds Ratio (tofersen/placebo)		0.63
SE of log (OR)		0.518
95% CI		(0.229, 1.741)
p-value		0.3740
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.081
95% CI		(-0.229, 0.090)
p-value		0.3926

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		1.67
SE of log (RR)		0.626
95% CI		(0.489, 5.683)
p-value		0.4144
OR - Odds Ratio (tofersen/placebo)		1.77
SE of log (OR)		0.693
95% CI		(0.456, 6.896)
p-value		0.4078
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.062
95% CI		(-0.065, 0.176)
p-value		0.3664

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Muscular weakness

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		0.71
SE of log (RR)		0.449
95% CI		(0.297, 1.721)
p-value		0.4532
OR - Odds Ratio (tofersen/placebo)		0.67
SE of log (OR)		0.542
95% CI		(0.231, 1.932)
p-value		0.4567
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.078
95% CI		(-0.208, 0.096)
p-value		0.4737

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Paraesthesia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		0.71
SE of log (RR)		0.449
95% CI		(0.297, 1.721)
p-value		0.4532
OR - Odds Ratio (tofersen/placebo)		0.67
SE of log (OR)		0.542
95% CI		(0.231, 1.932)
p-value		0.4567
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.078
95% CI		(-0.208, 0.096)
p-value		0.4737

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Pyrexia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.56
SE of log (RR)		0.441
95% CI		(0.237, 1.335)
p-value		0.1920
OR - Odds Ratio (tofersen/placebo)		0.50
SE of log (OR)		0.536
95% CI		(0.175, 1.431)
p-value		0.1963
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.079
95% CI		(-0.253, 0.059)
p-value		0.2214

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Upper respiratory tract infection

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		2.25
SE of log (RR)		0.755
95% CI		(0.513, 9.874)
p-value		0.2825
OR - Odds Ratio (tofersen/placebo)		2.43
SE of log (OR)		0.810
95% CI		(0.496, 11.884)
p-value		0.2734
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.055
95% CI		(-0.037, 0.176)
p-value		0.2031

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.90
SE of log (RR)		0.519
95% CI		(0.325, 2.489)
p-value		0.8392
OR - Odds Ratio (tofersen/placebo)		0.89
SE of log (OR)		0.599
95% CI		(0.274, 2.867)
p-value		0.8395
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.070
95% CI		(-0.150, 0.122)
p-value		0.8418

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Dysphagia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	1 (2.8)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		4.00
SE of log (RR)		1.041
95% CI		(0.520, 30.762)
p-value		0.1829
OR - Odds Ratio (tofersen/placebo)		4.38
SE of log (OR)		1.081
95% CI		(0.526, 36.423)
p-value		0.1723
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.046
95% CI		(-0.007, 0.174)
p-value		0.0704

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Contusion

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.57
SE of log (RR)		0.476
95% CI		(0.225, 1.451)
p-value		0.2393
OR - Odds Ratio (tofersen/placebo)		0.52
SE of log (OR)		0.564
95% CI		(0.171, 1.564)
p-value		0.2432
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.076
95% CI		(-0.232, 0.065)
p-value		0.2706

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Pleocytosis

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.645
95% CI		(0.376, 4.725)
p-value		0.6558
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.710
95% CI		(0.342, 5.530)
p-value		0.6538
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.059
95% CI		(-0.088, 0.144)
p-value		0.6384

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Psychiatric disorders/Anxiety

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.577
95% CI		(0.323, 3.101)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.650
95% CI		(0.280, 3.572)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.064
95% CI		(-0.126, 0.126)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Cough

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.645
95% CI		(0.376, 4.725)
p-value		0.6558
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.710
95% CI		(0.342, 5.530)
p-value		0.6538
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.059
95% CI		(-0.088, 0.144)
p-value		0.6384

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.88
SE of log (RR)		0.593
95% CI		(0.274, 2.795)
p-value		0.8217
OR - Odds Ratio (tofersen/placebo)		0.86
SE of log (OR)		0.663
95% CI		(0.235, 3.159)
p-value		0.8221
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.063
95% CI		(-0.137, 0.109)
p-value		0.8254

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Nasopharyngitis

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	9 (25.0)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.33
SE of log (RR)		0.486
95% CI		(0.129, 0.864)
p-value		0.0238
OR - Odds Ratio (tofersen/placebo)		0.27
SE of log (OR)		0.574
95% CI		(0.088, 0.841)
p-value		0.0237
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.17
SE of ARR		0.079
95% CI		(-0.322, -0.011)
p-value		0.0353

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Neck pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.540
95% CI		(0.173, 1.441)
p-value		0.1993
OR - Odds Ratio (tofersen/placebo)		0.45
SE of log (OR)		0.618
95% CI		(0.135, 1.526)
p-value		0.2020
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.070
95% CI		(-0.221, 0.054)
p-value		0.2348

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Psychiatric disorders/Insomnia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.612
95% CI		(0.226, 2.491)
p-value		0.6385
OR - Odds Ratio (tofersen/placebo)		0.73
SE of log (OR)		0.680
95% CI		(0.192, 2.760)
p-value		0.6398
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.062
95% CI		(-0.149, 0.093)
p-value		0.6525

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Urinary tract infection

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.33
SE of log (RR)		0.612
95% CI		(0.100, 1.107)
p-value		0.0728
OR - Odds Ratio (tofersen/placebo)		0.29
SE of log (OR)		0.682
95% CI		(0.077, 1.119)
p-value		0.0726
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.068
95% CI		(-0.244, 0.022)
p-value		0.1009

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Metabolism and nutrition disorders/Decreased appetite

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Joint swelling

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.40
SE of log (RR)		0.639
95% CI		(0.114, 1.400)
p-value		0.1516
OR - Odds Ratio (tofersen/placebo)		0.36
SE of log (OR)		0.705
95% CI		(0.092, 1.452)
p-value		0.1525
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.064
95% CI		(-0.208, 0.041)
p-value		0.1904

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Gastrointestinal disorders/Abdominal distension

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post procedural complication

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Hypoaesthesia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.30
SE of log (RR)		0.701
95% CI		(0.076, 1.186)
p-value		0.0860
OR - Odds Ratio (tofersen/placebo)		0.27
SE of log (OR)		0.762
95% CI		(0.061, 1.199)
p-value		0.0852
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.062
95% CI		(-0.219, 0.025)
p-value		0.1184

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Diarrhoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.09
SE of log (RR)		0.741
95% CI		(0.021, 0.389)
p-value		0.0012
OR - Odds Ratio (tofersen/placebo)		0.06
SE of log (OR)		0.803
95% CI		(0.013, 0.313)
p-value		0.0007
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.28
SE of ARR		0.079
95% CI		(-0.433, -0.123)
p-value		0.0005

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Skin laceration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.13
SE of log (RR)		1.099
95% CI		(0.014, 1.078)
p-value		0.0585
OR - Odds Ratio (tofersen/placebo)		0.11
SE of log (OR)		1.138
95% CI		(0.012, 1.049)
p-value		0.0551
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.054
95% CI		(-0.203, 0.009)
p-value		0.0727

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 16JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 1	8 (22.2)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.456
95% CI		(0.204, 1.223)
p-value		0.1289
OR - Odds Ratio (tofersen/placebo)		0.44
SE of log (OR)		0.549
95% CI		(0.149, 1.283)
p-value		0.1321
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.079
95% CI		(-0.265, 0.043)
p-value		0.1573

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 2	13 (36.1)	33 (45.8)
RR - Relative Risk (tofersen/placebo)		1.27
SE of log (RR)		0.256
95% CI		(0.768, 2.096)
p-value		0.3518
OR - Odds Ratio (tofersen/placebo)		1.50
SE of log (OR)		0.420
95% CI		(0.657, 3.409)
p-value		0.3366
ARR - Absolute Risk Reduction (tofersen/placebo)		0.10
SE of ARR		0.099
95% CI		(-0.097, 0.292)
p-value		0.3274

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 3	8 (22.2)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		1.06
SE of log (RR)		0.377
95% CI		(0.507, 2.225)
p-value		0.8723
OR - Odds Ratio (tofersen/placebo)		1.08
SE of log (OR)		0.488
95% CI		(0.416, 2.813)
p-value		0.8719
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.085
95% CI		(-0.154, 0.181)
p-value		0.8709

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 4	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 5	6 (16.7)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.486
95% CI		(0.289, 1.944)
p-value		0.5538
OR - Odds Ratio (tofersen/placebo)		0.71
SE of log (OR)		0.572
95% CI		(0.233, 2.191)
p-value		0.5563
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.073
95% CI		(-0.185, 0.102)
p-value		0.5699

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-maxctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any serious event	12 (33.3)	31 (43.1)
RR - Relative Risk (tofersen/placebo)		1.29
SE of log (RR)		0.272
95% CI		(0.758, 2.201)
p-value		0.3465
OR - Odds Ratio (tofersen/placebo)		1.51
SE of log (OR)		0.426
95% CI		(0.656, 3.487)
p-value		0.3319
ARR - Absolute Risk Reduction (tofersen/placebo)		0.10
SE of ARR		0.098
95% CI		(-0.095, 0.289)
p-value		0.3205

Source: biib067/valueaccess/amnog/t-sae-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		0.94
SE of log (RR)		0.387
95% CI		(0.439, 2.003)
p-value		0.8677
OR - Odds Ratio (tofersen/placebo)		0.92
SE of log (OR)		0.495
95% CI		(0.349, 2.430)
p-value		0.8680
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.084
95% CI		(-0.179, 0.151)
p-value		0.8690

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Infections and infestations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	11 (15.3)
RR - Relative Risk (tofersen/placebo)		0.79
SE of log (RR)		0.438
95% CI		(0.333, 1.855)
p-value		0.5822
OR - Odds Ratio (tofersen/placebo)		0.75
SE of log (OR)		0.534
95% CI		(0.263, 2.126)
p-value		0.5847
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.078
95% CI		(-0.195, 0.112)
p-value		0.5952

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Gastrointestinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.791
95% CI		(0.319, 7.064)
p-value		0.6080
OR - Odds Ratio (tofersen/placebo)		1.55
SE of log (OR)		0.843
95% CI		(0.296, 8.071)
p-value		0.6057
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.050
95% CI		(-0.071, 0.126)
p-value		0.5799

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Nervous system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.701
95% CI		(0.211, 3.294)
p-value		0.7949
OR - Odds Ratio (tofersen/placebo)		0.82
SE of log (OR)		0.761
95% CI		(0.185, 3.645)
p-value		0.7953
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.055
95% CI		(-0.122, 0.094)
p-value		0.8005

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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General disorders and administration site conditions

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-soc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 13JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

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Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.677
95% CI		(0.265, 3.769)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.739
95% CI		(0.235, 4.253)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.056
95% CI		(-0.111, 0.111)
p-value		1.0000

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.60
SE of log (RR)		0.570
95% CI		(0.196, 1.834)
p-value		0.3702
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.643
95% CI		(0.160, 1.989)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.066
95% CI		(-0.185, 0.074)
p-value		0.4014

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Acute respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	[redacted]
RR - Relative Risk (tofersen/placebo)		5.58
SE of log (RR)		1.463
95% CI		(0.317, 98.127)
p-value		0.2403
OR - Odds Ratio (tofersen/placebo)		5.95
SE of log (OR)		1.491
95% CI		(0.320, 110.610)
p-value		0.2318
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.036
95% CI		(-0.009, 0.133)
p-value		0.0881

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Gastrointestinal disorders/Dysphagia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Pulmonary embolism

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.842
95% CI		(0.192, 5.205)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.891
95% CI		(0.174, 5.735)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.047
95% CI		(-0.092, 0.092)
p-value		1.0000

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		0.10
SE of log (RR)		1.536
95% CI		(0.005, 2.058)
p-value		0.1362
OR - Odds Ratio (tofersen/placebo)		0.10
SE of log (OR)		1.563
95% CI		(0.004, 2.037)
p-value		0.1324
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.042
95% CI		(-0.144, 0.022)
p-value		0.1519

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-sae-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	14 (38.9)	30 (41.7)
RR - Relative Risk (tofersen/placebo)		1.07
SE of log (RR)		0.251
95% CI		(0.655, 1.753)
p-value		0.7836
OR - Odds Ratio (tofersen/placebo)		1.12
SE of log (OR)		0.417
95% CI		(0.496, 2.542)
p-value		0.7819
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.100
95% CI		(-0.168, 0.224)
p-value		0.7809

Source: biib067/valueaccess/amnog/t-ae-ctc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	5 (13.9)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.60
SE of log (RR)		0.570
95% CI		(0.196, 1.834)
p-value		0.3702
OR - Odds Ratio (tofersen/placebo)		0.56
SE of log (OR)		0.643
95% CI		(0.160, 1.989)
p-value		0.3729
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.066
95% CI		(-0.185, 0.074)
p-value		0.4014

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	2 (5.6)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.842
95% CI		(0.192, 5.205)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.891
95% CI		(0.174, 5.735)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.047
95% CI		(-0.092, 0.092)
p-value		1.0000

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Acute respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Pulmonary embolism

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	1 (2.8)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		2.00
SE of log (RR)		1.099
95% CI		(0.232, 17.247)
p-value		0.5283
OR - Odds Ratio (tofersen/placebo)		2.06
SE of log (OR)		1.137
95% CI		(0.222, 19.126)
p-value		0.5254
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.038
95% CI		(-0.048, 0.103)
p-value		0.4701

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	3 (8.3)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.33
SE of log (RR)		0.890
95% CI		(0.058, 1.907)
p-value		0.2169
OR - Odds Ratio (tofersen/placebo)		0.31
SE of log (OR)		0.937
95% CI		(0.050, 1.972)
p-value		0.2167
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.050
95% CI		(-0.153, 0.042)
p-value		0.2662

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

Gastrointestinal disorders/Constipation

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	[redacted]	
RR - Relative Risk (tofersen/placebo)		0.10
SE of log (RR)		1.536
95% CI		(0.005, 2.058)
p-value		0.1362
OR - Odds Ratio (tofersen/placebo)		0.10
SE of log (OR)		1.563
95% CI		(0.004, 2.037)
p-value		0.1324
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.042
95% CI		(-0.144, 0.022)
p-value		0.1519

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 14JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event leading to drug discontinuation - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with at least one adverse event leading to drug discontinuation	6 (16.7)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		1.08
SE of log (RR)		0.449
95% CI		(0.449, 2.614)
p-value		0.8586
OR - Odds Ratio (tofersen/placebo)		1.10
SE of log (OR)		0.542
95% CI		(0.381, 3.188)
p-value		0.8582
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.077
95% CI		(-0.137, 0.165)
p-value		0.8567

Source: biib067/valueaccess/amnog/t-ae-disc-event-cl.sas **Data Cutoff:** 15JUL2022 **Run Date:** 12JUL2023

233AS101 and 233AS102 ISS: Adverse events that led to discontinuation of study drug by system organ class and preferred term for pooled groups CL1 and CL2 - safety population

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	CL1: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	CL2: 233AS102 (Part C subjects) tofersen treated period
	early-start tofersen 100 mg (N=72) n (%)	delayed-start tofersen 100 mg (N=32) n (%)
Number of subjects with any event that led to discontinuation	12 (16.7)	6 (18.8)
Respiratory, thoracic and mediastinal disorders	7 (9.7)	5 (15.6)
Respiratory failure	4 (5.6)	5 (15.6)
Pulmonary embolism	[redacted]	
Respiratory arrest		
Cardiac disorders	1 (1.4)	1 (3.1)
Cardiac arrest	[redacted]	
Cardiac failure congestive		
Nervous system disorders	[redacted]	
Amyotrophic lateral sclerosis		
Gastrointestinal disorders	[redacted]	
Salivary hypersecretion		
General disorders and administration site conditions	[redacted]	
Sudden death		
Infections and infestations	1 (1.4)	0
Myelitis	1 (1.4)	0
Injury, poisoning and procedural complications	[redacted]	

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 24.0).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla2/t-ae-socpt-cl.sas:t-ae-socpt-cl-disc.rtf **Run Date:** 16MAR2022

233AS101 and 233AS102 ISS: Adverse events that led to discontinuation of study drug by system organ class and preferred term for pooled groups CL1 and CL2 - safety population

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	CL1: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	CL2: 233AS102 (Part C subjects) tofersen treated period
	early-start tofersen 100 mg (N=72) n (%)	delayed-start tofersen 100 mg (N=32) n (%)
Meningitis chemical	1 (1.4)	0
Musculoskeletal and connective tissue disorders	[redacted]	
Muscular weakness		

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 24.0).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla2/t-ae-socpt-cl.sas:t-ae-socpt-cl-disc.rtf **Run Date:** 16MAR2022

233AS101 and 233AS102 ISS: Adverse events that led to withdrawal from study by system organ class and preferred term for pooled groups CL1 and CL2 - safety population

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	CL1: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	CL2: 233AS102 (Part C subjects) tofersen treated period
	early-start tofersen 100 mg (N=72) n (%)	delayed-start tofersen 100 mg (N=32) n (%)
Number of subjects with any event that led to withdrawal	11 (15.3)	7 (21.9)
Respiratory, thoracic and mediastinal disorders	6 (8.3)	5 (15.6)
Respiratory failure	[redacted]	
Respiratory arrest		
Cardiac disorders	1 (1.4)	1 (3.1)
Cardiac arrest	[redacted]	
Cardiac failure congestive		
Infections and infestations	1 (1.4)	1 (3.1)
Pneumonia	[redacted]	
Myelitis		
General disorders and administration site conditions	[redacted]	
Sudden death		
Injury, poisoning and procedural complications	1 (1.4)	0
Meningitis chemical	1 (1.4)	0
Musculoskeletal and connective tissue disorders	[redacted]	
Muscular weakness		

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 24.0).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla2/t-ae-socpt-cl.sas:t-ae-socpt-cl-wd.rtf **Run Date:** 16MAR2022

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233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

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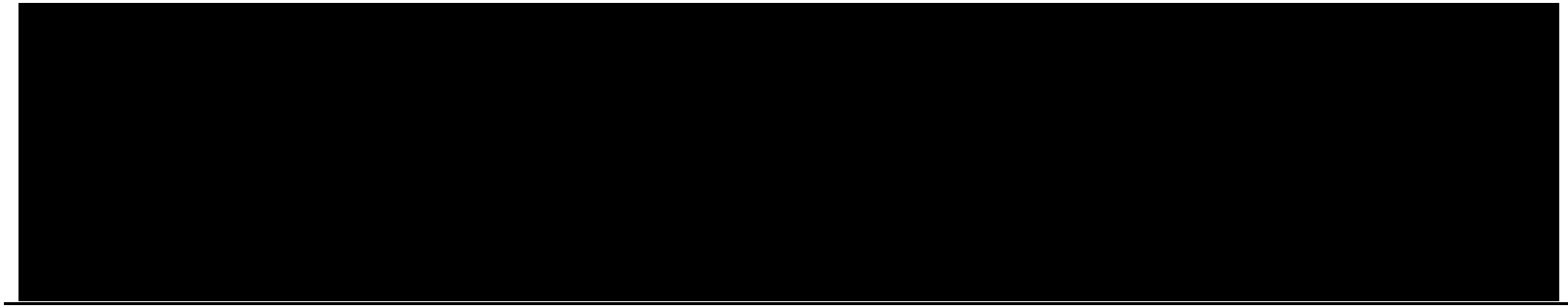
	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects with an event of death or permanent ventilation	9 (25.0)	16 (22.2)
Death	5 (13.9)	7 (9.7)
Permanent ventilation	4 (11.1)	9 (12.5)
Number of days with ventilation use for at least 22 hours per day		
n	4	10
Mean (SD)	101.50 (82.706)	104.20 (133.704)
Median	98.50	56.50
Q1,Q3	38.00, 165.00	27.00, 90.00
Min, Max	8.0, 201.0	4.0, 455.0



NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-vafs-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
[redacted]		

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-vafs-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects who were censored	27 (75.0)	56 (77.8)
Time to death or permanent ventilation (95% CI) (weeks) (a)		
5th percentile	27.4 (24.4 , 61.9)	28.0 (16.3 , 48.0)
10th percentile	57.3 (24.4 , 76.0)	48.0 (16.3 , 98.6)
25th percentile	115.4 (33.9, NE)	171.0 (82.1, NE)
50th percentile	NE (135.6, NE)	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects with an event of death or permanent ventilation by		
26 weeks	0.030	0.029
52 weeks	0.092	0.105
78 weeks	0.236	0.121
104 weeks	0.236	0.203
130 weeks	0.281	0.223
156 weeks	0.347	0.223
182 weeks	0.347	0.273
208 weeks	NA	NA

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-vafs-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Summary of time to death or permanent ventilation for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
p-value (tofersen - placebo) (b)		0.1685
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.8591
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.47 (0.196, 1.108)
p-value (tofersen - placebo) (d)		0.0842

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included. Number of days with ventilation use for at least 22 hours per day is summarized based on the collected ediary or ventilation log.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-vafs-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death or permanent ventilation for pooled group CL - ITT population

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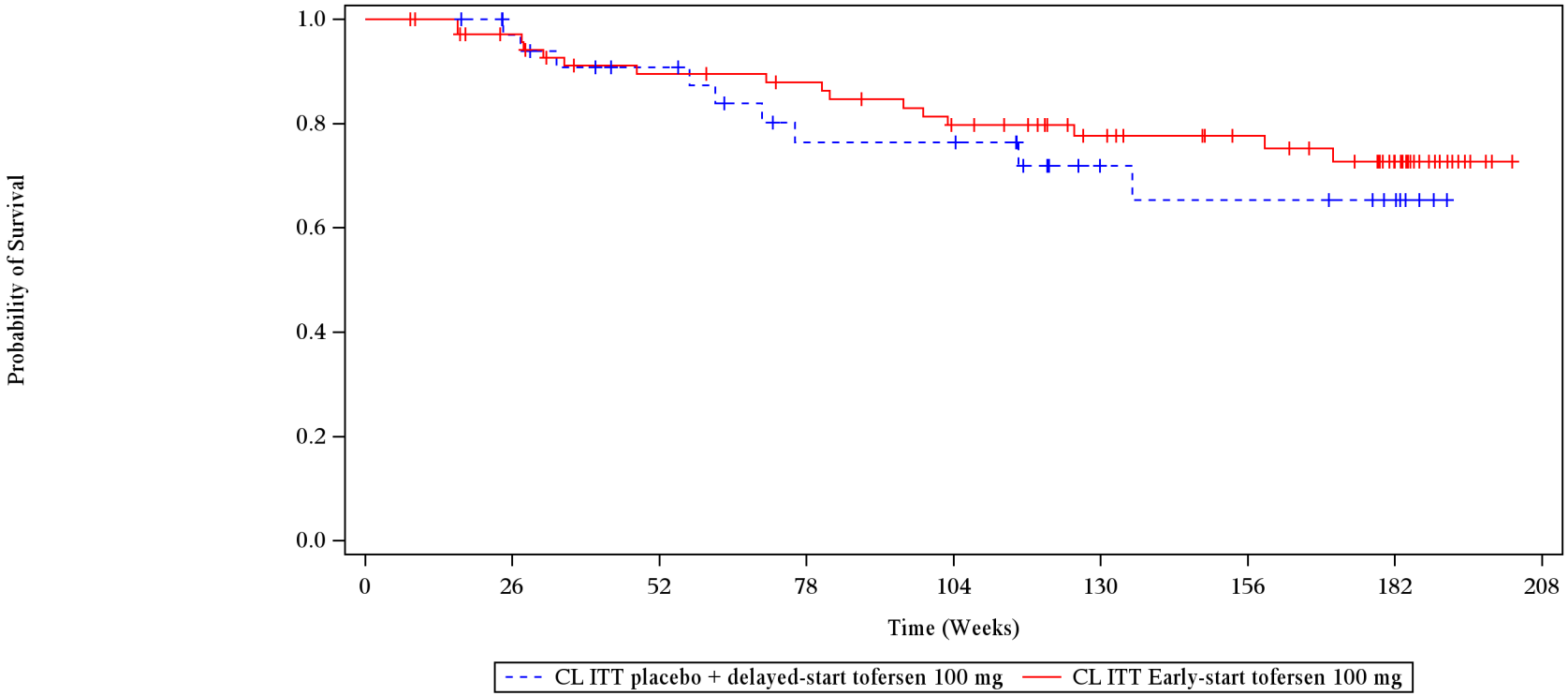

At Risk:

CL ITT placebo + delayed-start tofersen 100 mg	36	32	27	20	20	11	10	7	0
CL ITT Early-start tofersen 100 mg	72	65	57	54	47	38	32	20	0

NOTE 1: Time to death or permanent ventilation is defined as the time from first dose to death or permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/ise/ise-bla4/f-vafs-km-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISE: Summary of time to death since 233AS101 baseline for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects who died	7 (19.4)	11 (15.3)
Number of subjects who were censored	29 (80.6)	61 (84.7)
Time to death (95% CI) (weeks)		
5th percentile	57.1 (33.9 , 61.9)	52.1 (16.3 , 82.1)
10th percentile	60.7 (33.9 , 115.4)	82.1 (31.4 , 171.0)
25th percentile	135.6 (60.7, NE)	NE (125.3, NE)
50th percentile	NE (135.6, NE)	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects who died by		
26 weeks	0.000	0.014
52 weeks	0.031	0.046
78 weeks	0.176	0.095
104 weeks	0.176	0.129
130 weeks	0.225	0.149
156 weeks	NA	NA
182 weeks	NA	NA
208 weeks	NA	NA

NOTE 1: Time to death as the time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-surv-sum-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Summary of time to death since 233AS101 baseline for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
p-value (tofersen - placebo) (b)		0.1224
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.6618
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.36 (0.131 ,1.017)
p-value (tofersen - placebo) (d)		0.0538

NOTE 1: Time to death as the time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-surv-sum-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death since 233AS101 baseline for pooled group CL - ITT population

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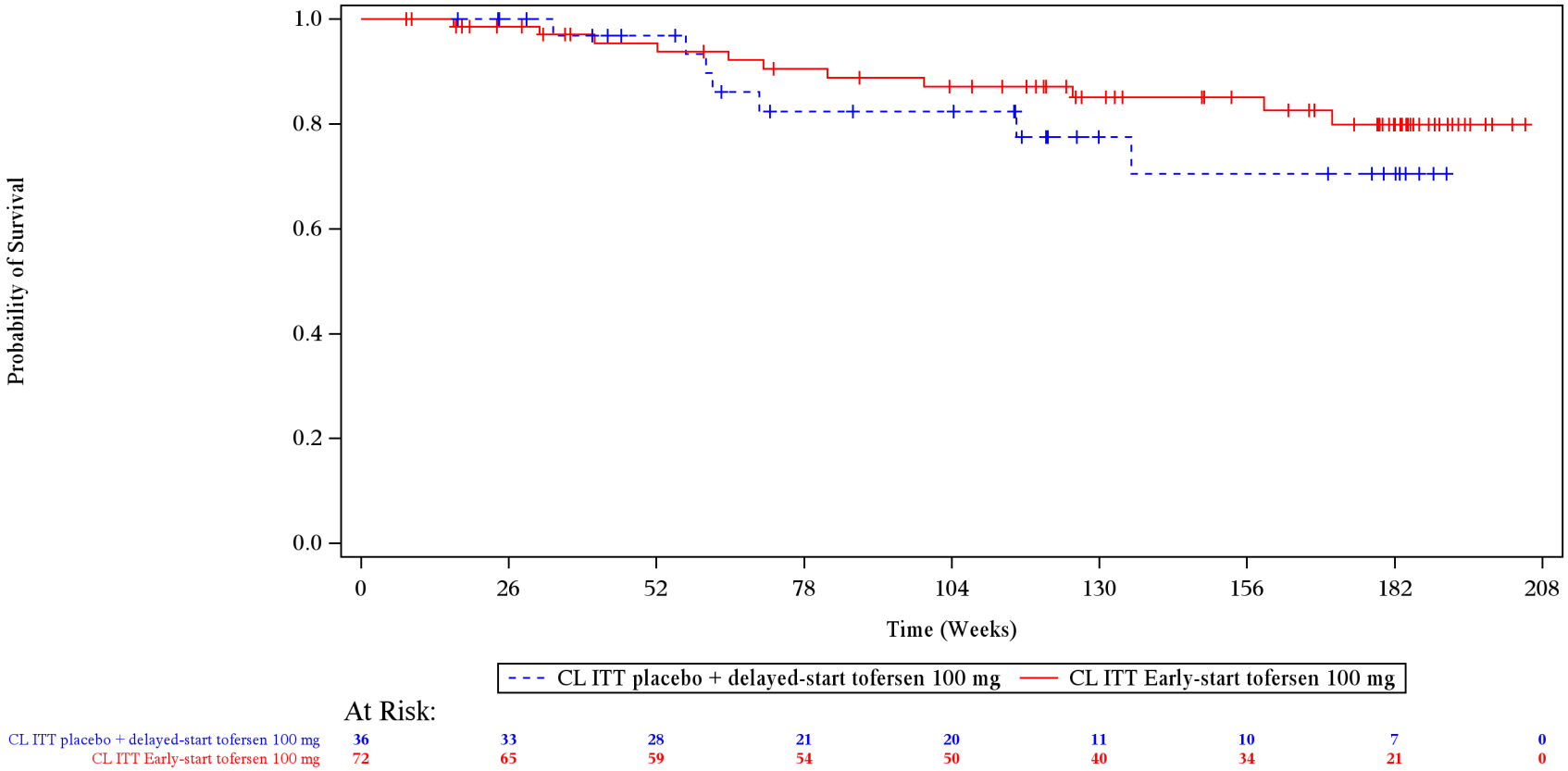

NOTE 1: Time to death is defined as the time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/ise/ise-bla4/f-surv-km-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 24MAY2023

233AS101 and 233AS102 ISE: Summary of time to permanent ventilation - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects with permanent ventilation	4 (11.1)	9 (12.5)
Number of subjects who were censored	32 (88.9)	63 (87.5)
Time to permanent ventilation (95% CI) (weeks) (a)		
5th percentile	27.4 (NE, 76.0)	35.1 (16.3 , 95.1)
10th percentile	76.0 (24.4, NE)	95.1 (27.7, NE)
25th percentile	NE (57.3, NE)	NE (103.0, NE)
50th percentile	NA	NA
75th percentile	NA	NA

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog4/t-cf-vafsp-sum-clitt-bpnfl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 02AUG2023

233AS101 and 233AS102 ISE: Summary of time to permanent ventilation - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Estimated proportion (a) of subjects with permanent ventilation by		
26 weeks	0.030	0.014
52 weeks	0.061	0.077
78 weeks	0.140	0.077
104 weeks	0.140	0.147
130 weeks	0.140	0.147
p-value (tofersen - placebo) (b)		0.5901
log-rank stratified by randomization factors: p-value (tofersen - placebo) (c)		0.7630
Hazard ratio (tofersen - placebo) and 95% CI (d)		0.59 (0.169, 2.043)
p-value (tofersen - placebo) (d)		0.4024

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog4/t-cf-vafsp-sum-clitt-bpnfl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 02AUG2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to permanent ventilation for pooled group CL - ITT population

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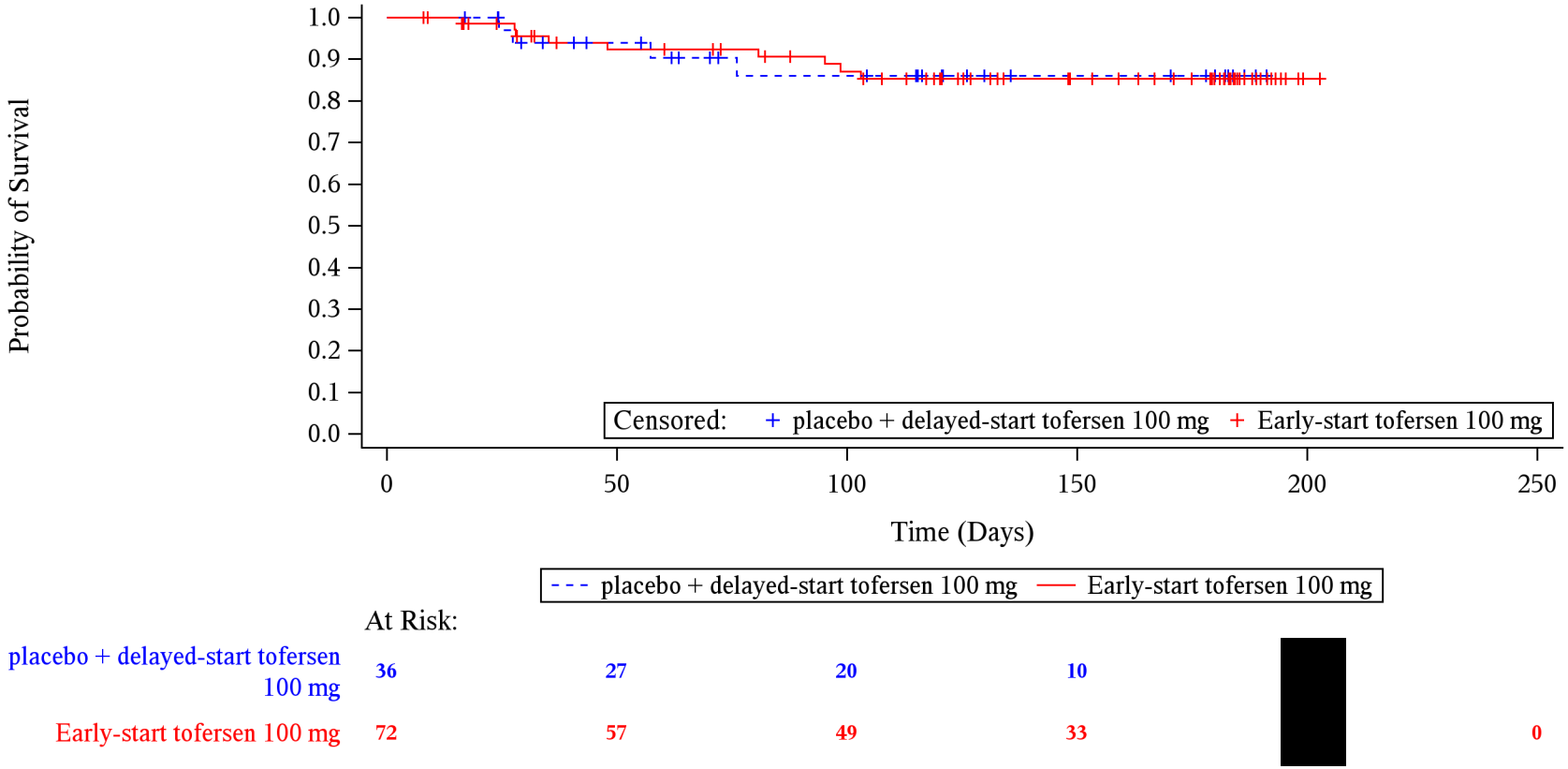

NOTE 1: Time to permanent ventilation is defined as the time from first dose to permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/valueaccess/amnog4/f-surv-km-vafsp-itt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 02AUG2023

233AS101 and 233AS102 ISE: Summary of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - ITT population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with an event	14 (38.9)	24 (33.3)
Death	5 (13.9)	7 (9.7)
Permanent ventilation	4 (11.1)	9 (12.5)
Withdrawal due to disease progression	5 (13.9)	8 (11.1)
Number of subjects who were censored	22 (61.1)	48 (66.7)
Time to event (95% CI) (weeks) (a)		
5th percentile	24.3 (17.0 , 33.9)	17.7 (8.9 , 35.1)
10th percentile	27.4 (17.0 , 55.3)	31.4 (16.3 , 70.9)
25th percentile	61.9 (27.4 , 115.4)	98.6 (48.0 , 159.0)
50th percentile	NE (70.1, NE)	NE (171.0, NE)
75th percentile	NA	NA

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-phoc-vafs-wddp-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 23MAY2023

233AS101 and 233AS102 ISE: Summary of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Estimated proportion (a) of subjects with an event by		
26 weeks	0.085	0.057
52 weeks	0.173	0.145
78 weeks	0.358	0.190
104 weeks	0.358	0.281
130 weeks	0.396	0.314
156 weeks	0.451	0.334
182 weeks	0.451	0.378
208 weeks	NA	NA
p-value (tofersen - placebo) (b)		0.0866
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.7027
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.50 (0.248 ,0.992)
p-value (tofersen - placebo) (d)		0.0475

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-phoc-vafs-wddp-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 23MAY2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death, permanent ventilation or withdrawal due to disease progression for pooled group CL - ITT population

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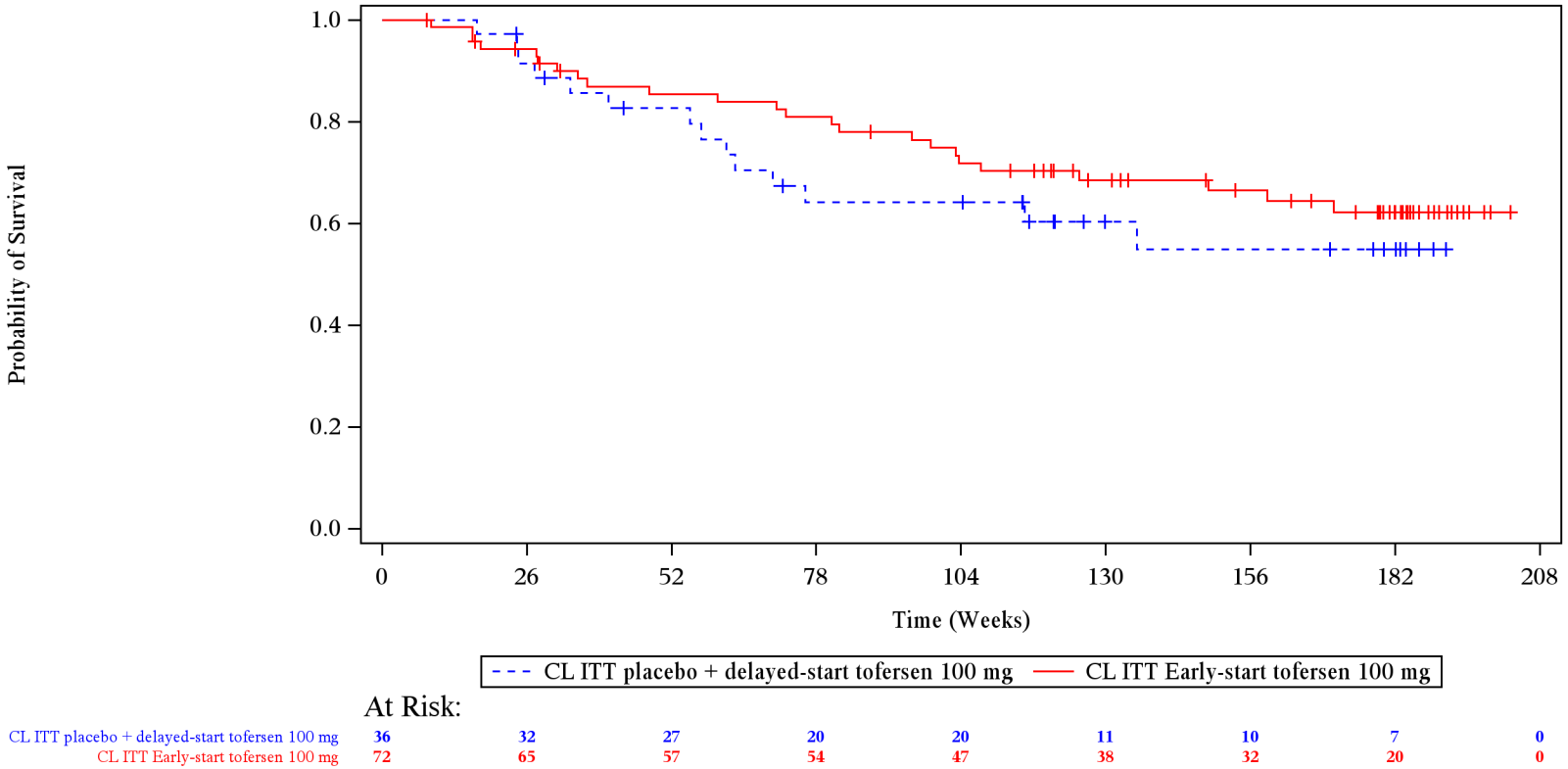

At Risk:

CL ITT placebo + delayed-start tofersen 100 mg	36	32	27	20	20	11	10	7	0
CL ITT Early-start tofersen 100 mg	72	65	57	54	47	38	32	20	0

NOTE 1: Time to event is defined as the time from first dose to death, permanent ventilation (>= 22 hours of mechanical ventilation [invasive or noninvasive] per day for >= 21 consecutive days), or withdrawal from the study due to disease progression, whichever comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.

Source: biib067/ise/ise-bla4/f-phoc-vafs-wddp-km-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISE: Summary of time to withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects withdrew due to disease progression	7 (19.4)	10 (13.9)
Number of subjects who were censored	29 (80.6)	62 (86.1)
Time to withdrawal due to disease progression (95% CI) (weeks) (a)		
5th percentile	24.3 (17.0 , 55.3)	35.9 (8.9 , 72.6)
10th percentile	45.9 (17.0 , 86.6)	72.6 (17.7, NE)
25th percentile	NE (45.9, NE)	NE (107.6, NE)
50th percentile	NA	NA
75th percentile	NA	NA
Estimated proportion (a) of subjects withdrew due to disease progression by		
26 weeks	0.056	0.043
52 weeks	0.118	0.074
78 weeks	0.185	0.106
104 weeks	0.224	0.124
130 weeks	0.224	0.142
156 weeks	0.224	0.165
182 weeks	0.224	0.165
208 weeks	NA	NA
p-value (tofersen - placebo) (b)		0.1597
log-rank stratified by randomization factors: p-value (tofersen - placebo) (c)		0.5538
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.51 (0.185 ,1.400)

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog4/t-cf-vwdp-sum-clitt.sas **Data Cutoff:** **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Summary of time to withdrawal due to disease progression for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
p-value (tofersen - placebo) (d)		0.1906

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
(a) Based on Kaplan-Meier product limit method.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/valueaccess/amnog4/t-cf-vwdp-sum-clitt.sas **Data Cutoff:** **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to time to early withdrawal due to disease progression for pooled group CL - ITT population

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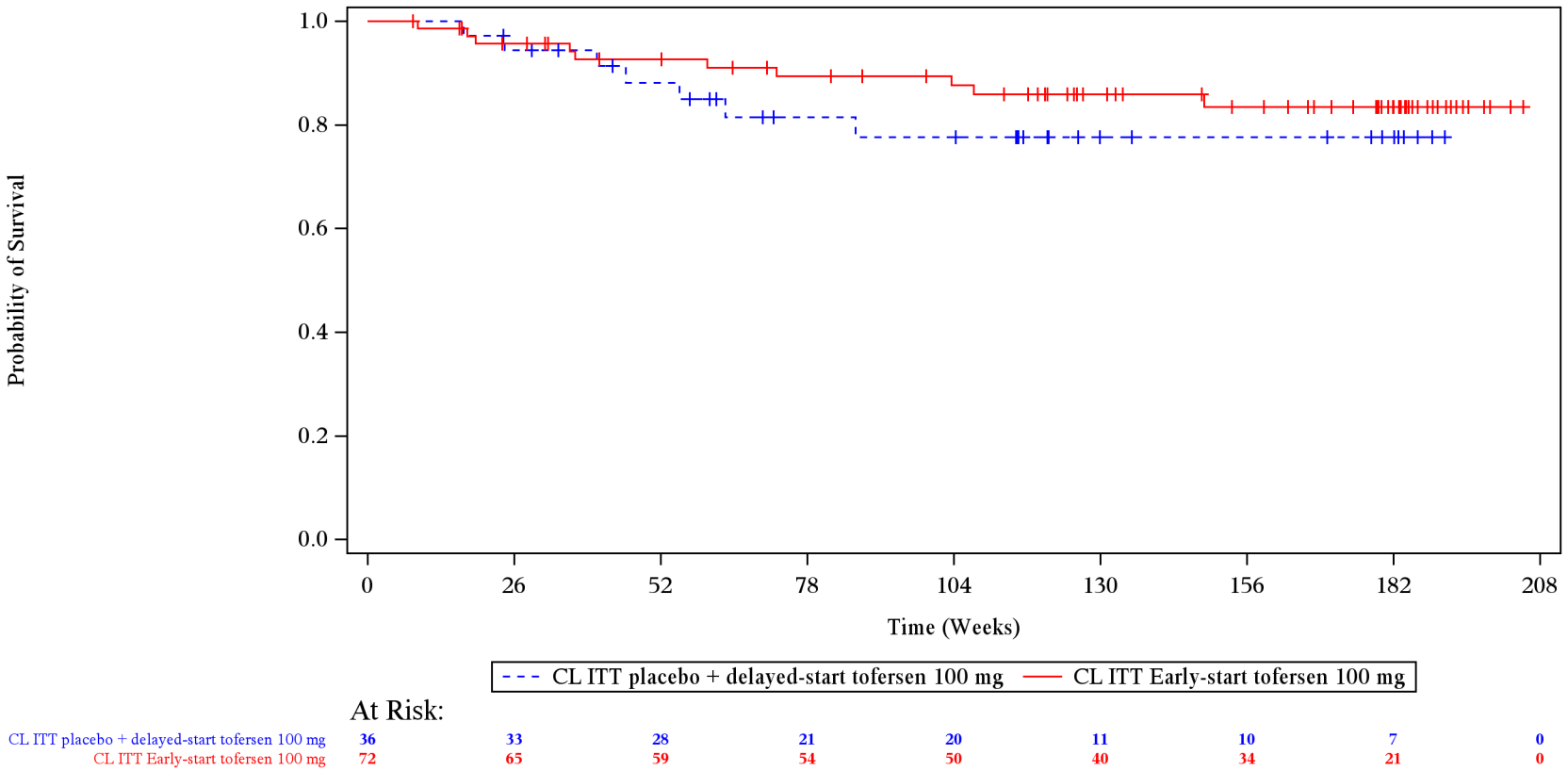

NOTE 1: Time to withdrawal due to disease progression is defined as the time from first dose to early withdrawal from the study due to disease progression. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
NOTE 2: + indicates censored data.
Source: biib067/valueaccess/amnog4/f-surv-km-vwdp-clitt.sas **Data Cutoff:** **Run Date:** 05OCT2023

233AS101 and 233AS102 ISE: Summary of time to death since ALS symptom onset for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Number of subjects who died	7 (19.4)	11 (15.3)
Number of subjects who were censored	29 (80.6)	61 (84.7)
Time to death (95% CI) (weeks)		
5th percentile	73.1 (73.1 , 113.1)	82.0 (45.9 , 106.7)
10th percentile	97.4 (73.1 , 183.3)	105.3 (45.9 , 141.0)
25th percentile	183.3 (73.1 , 491.4)	209.9 (106.7, NE)
50th percentile	491.4 (183.3, NE)	NE (325.3, NE)
75th percentile	NE (491.4, NE)	NA

NOTE 1: Time to death is defined as the time from ALS symptom onset to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method adjusted for delayed entry.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-surv-oset-sum-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 23MAY2023

233AS101 and 233AS102 ISE: Summary of time to death since ALS symptom onset for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Estimated proportion (a) of subjects who died by		
52 weeks	0.000	0.031
104 weeks	0.118	0.077
156 weeks	0.229	0.218
208 weeks	0.302	0.218
260 weeks	0.368	0.250
312 weeks	0.368	0.250
364 weeks	0.368	0.322
416 weeks	0.368	0.322
468 weeks	0.368	0.322
520 weeks	0.617	0.322
572 weeks	0.617	0.322
624 weeks	0.617	0.322
676 weeks	0.617	0.322
728 weeks	0.617	0.322
780 weeks	0.617	0.322
832 weeks	0.617	0.322

NOTE 1: Time to death is defined as the time from ALS symptom onset to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method adjusted for delayed entry.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-surv-oset-sum-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 23MAY2023

233AS101 and 233AS102 ISE: Summary of time to death since ALS symptom onset for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
p-value (tofersen - placebo) (b)		0.1697
log-rank stratified by randomization factors : p-value (tofersen - placebo) (c)		0.8517
Hazard ratio (tofersen - placebo to tofersen) and 95% CI (d)		0.27 (0.084 ,0.853)
p-value (tofersen - placebo) (d)		0.0258

NOTE 1: Time to death is defined as the time from ALS symptom onset to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
(a) Based on Kaplan-Meier product limit method adjusted for delayed entry.
(b) Based on a log rank test stratified by median baseline plasma NfL.
(c) Based on a log rank test stratified by randomization factors, i.e. riluzole or edaravone use, and disease progression subgroup (mITT/non mITT)..
(d) Based on a Cox proportional hazards model adjusted for baseline plasma NfL, and riluzole or edaravone use.
Source: biib067/ise/ise-bla4/t-surv-oset-sum-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 23MAY2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of time to death since ALS symptom onset for pooled group CL - ITT population

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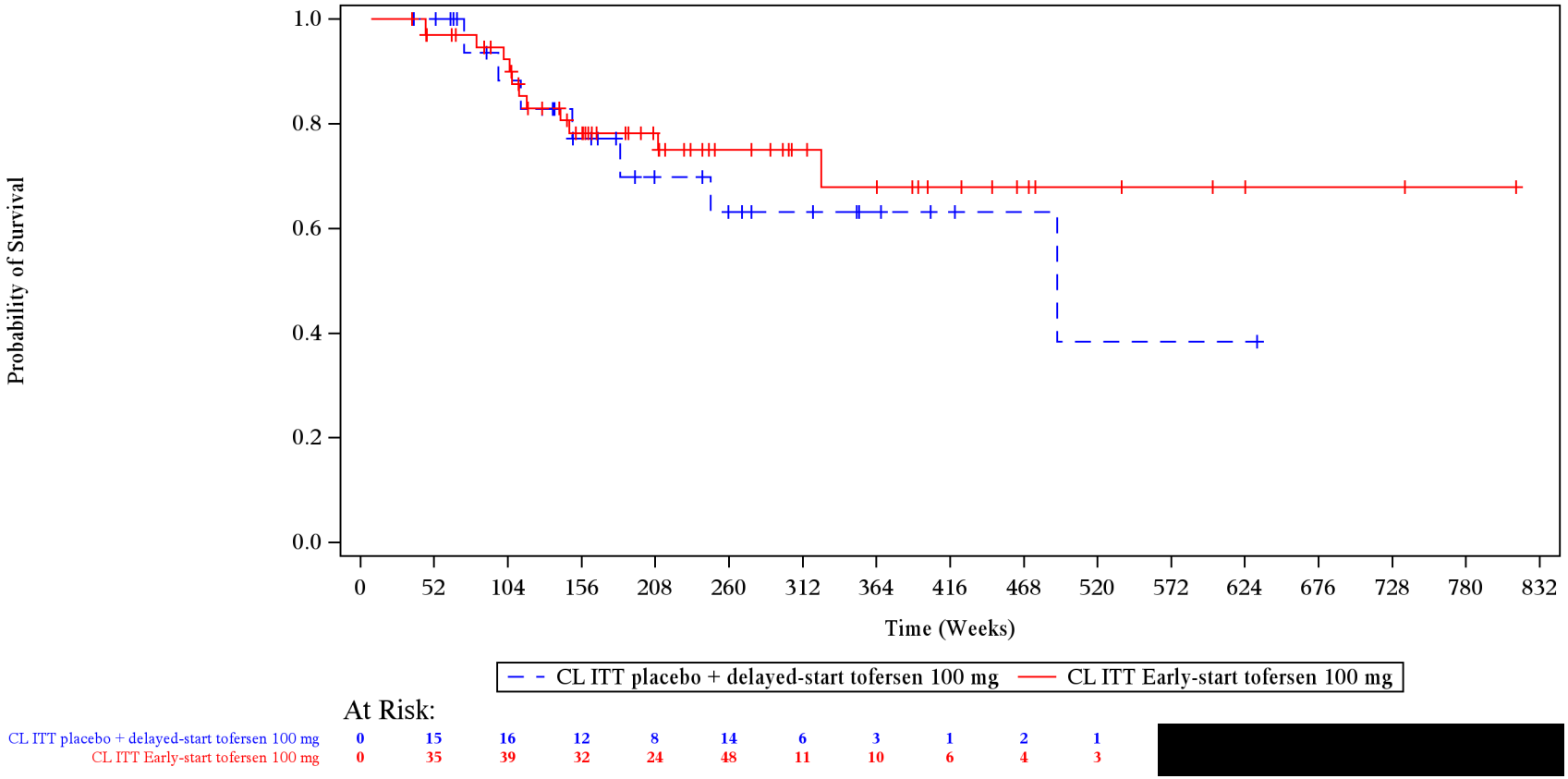

NOTE 1: Time to death is defined as the time from ALS symptom onset to death. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date. Only events that were adjudicated by the Endpoint Adjudication Committee are included.
NOTE 2: + indicates censored data.
Source: biib067/ise/ise-bla4/f-surv-oset-km-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-1.9	-1.4
SE	0.63	0.50
95% CI	(-3.14, -0.65)	(-2.37, -0.39)
LS mean difference (tofersen - placebo)		0.5
SE		0.70
95% CI		(-0.85, 1.88)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.31, 0.50)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-6.3	-4.2
SE	1.13	0.89
95% CI	(-8.49, -4.06)	(-5.91, -2.44)
LS mean difference (tofersen - placebo)		2.1
SE		1.24
95% CI		(-0.33, 4.52)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.19, 0.65)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-8.8	-5.7
SE	1.38	1.08
95% CI	(-11.45, -6.06)	(-7.86, -3.63)
LS mean difference (tofersen - placebo)		3.0
SE		1.51
95% CI		(0.05, 5.97)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.16, 0.74)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-9.6	-6.0
SE	1.49	1.17
95% CI	(-12.52, -6.69)	(-8.32, -3.73)
LS mean difference (tofersen - placebo)		3.6
SE		1.60
95% CI		(0.44, 6.72)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.15, 0.76)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	22 (61.1)	55 (76.4)
Number of imputed values per imputation	14 (38.9)	17 (23.6)
LS mean change from baseline	-10.7	-7.1
SE	1.61	1.27
95% CI	(-13.88, -7.56)	(-9.62, -4.65)
LS mean difference (tofersen - placebo)		3.6
SE		1.75
95% CI		(0.16, 7.01)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.22, 0.77)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	54 (75.0)
Number of imputed values per imputation	16 (44.4)	18 (25.0)
LS mean change from baseline	-11.0	-7.6
SE	1.74	1.35
95% CI	(-14.44, -7.62)	(-10.27, -4.97)
LS mean difference (tofersen - placebo)		3.4
SE		1.87
95% CI		(-0.26, 7.08)
p-value		0.0686
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.27, 0.76)
p-value		0.3423

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	21 (58.3)	51 (70.8)
Number of imputed values per imputation	15 (41.7)	21 (29.2)
LS mean change from baseline	-11.9	-8.5
SE	1.92	1.48
95% CI	(-15.65, -8.11)	(-11.45, -5.64)
LS mean difference (tofersen - placebo)		3.3
SE		2.06
95% CI		(-0.70, 7.37)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.29, 0.73)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 104		
Number of observations per imputation	20 (55.6)	49 (68.1)
Number of imputed values per imputation	16 (44.4)	23 (31.9)
LS mean change from baseline	-13.2	-9.5
SE	2.15	1.65
95% CI	(-17.45, -9.02)	(-12.75, -6.27)
LS mean difference (tofersen - placebo)		3.7
SE		2.27
95% CI		(-0.72, 8.17)
p-value		0.1004
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.29, 0.75)
p-value		0.3837

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.1	0.0
SE	0.17	0.13
95% CI	(-0.45, 0.20)	(-0.26, 0.25)
LS mean difference (tofersen - placebo)		0.1
SE		0.18
95% CI		(-0.24, 0.47)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.29, 0.53)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-0.5	-0.6
SE	0.27	0.21
95% CI	(-1.03, 0.03)	(-1.05, -0.22)
LS mean difference (tofersen - placebo)		-0.1
SE		0.30
95% CI		(-0.72, 0.45)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.53, 0.32)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-1.1	-1.2
SE	0.34	0.27
95% CI	(-1.81, -0.46)	(-1.74, -0.69)
LS mean difference (tofersen - placebo)		-0.1
SE		0.38
95% CI		(-0.82, 0.66)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.52, 0.37)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-1.7	-1.4
SE	0.46	0.38
95% CI	(-2.63, -0.84)	(-2.19, -0.71)
LS mean difference (tofersen - placebo)		0.3
SE		0.51
95% CI		(-0.72, 1.29)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.43, 0.47)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	22 (61.1)	55 (76.4)
Number of imputed values per imputation	14 (38.9)	17 (23.6)
LS mean change from baseline	-2.1	-2.0
SE	0.53	0.42
95% CI	(-3.13, -1.05)	(-2.78, -1.15)
LS mean difference (tofersen - placebo)		0.1
SE		0.59
95% CI		(-1.03, 1.28)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.54, 0.45)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	54 (75.0)
Number of imputed values per imputation	16 (44.4)	18 (25.0)
LS mean change from baseline	-2.3	-2.3
SE	0.55	0.42
95% CI	(-3.42, -1.26)	(-3.07, -1.43)
LS mean difference (tofersen - placebo)		0.1
SE		0.61
95% CI		(-1.11, 1.28)
p-value		0.8896
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.56, 0.47)
p-value		0.8567

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	21 (58.3)	51 (70.8)
Number of imputed values per imputation	15 (41.7)	21 (29.2)
LS mean change from baseline	-2.8	-2.6
SE	0.64	0.48
95% CI	(-4.02, -1.52)	(-3.57, -1.68)
LS mean difference (tofersen - placebo)		0.1
SE		0.70
95% CI		(-1.24, 1.52)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.56, 0.46)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Bulbar Function Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 104		
Number of observations per imputation	20 (55.6)	49 (68.1)
Number of imputed values per imputation	16 (44.4)	23 (31.9)
LS mean change from baseline	-2.9	-2.8
SE	0.67	0.51
95% CI	(-4.25, -1.61)	(-3.76, -1.77)
LS mean difference (tofersen - placebo)		0.2
SE		0.73
95% CI		(-1.27, 1.61)
p-value		0.8180
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.55, 0.49)
p-value		0.9034

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.6	-0.6
SE	0.23	0.18
95% CI	(-1.03, -0.12)	(-0.95, -0.23)
LS mean difference (tofersen - placebo)		0.0
SE		0.25
95% CI		(-0.52, 0.48)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.46, 0.36)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-2.1	-1.2
SE	0.38	0.30
95% CI	(-2.79, -1.32)	(-1.83, -0.67)
LS mean difference (tofersen - placebo)		0.8
SE		0.41
95% CI		(0.01, 1.62)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.12, 0.73)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.4	-1.6
SE	0.44	0.34
95% CI	(-3.29, -1.57)	(-2.26, -0.91)
LS mean difference (tofersen - placebo)		0.8
SE		0.48
95% CI		(-0.10, 1.78)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.19, 0.71)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-2.6	-1.6
SE	0.45	0.36
95% CI	(-3.51, -1.73)	(-2.28, -0.87)
LS mean difference (tofersen - placebo)		1.0
SE		0.48
95% CI		(0.10, 1.99)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.14, 0.77)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	22 (61.1)	55 (76.4)
Number of imputed values per imputation	14 (38.9)	17 (23.6)
LS mean change from baseline	-3.1	-1.8
SE	0.50	0.40
95% CI	(-4.07, -2.10)	(-2.63, -1.07)
LS mean difference (tofersen - placebo)		1.2
SE		0.54
95% CI		(0.18, 2.30)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.14, 0.85)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	54 (75.0)
Number of imputed values per imputation	16 (44.4)	18 (25.0)
LS mean change from baseline	-2.9	-2.0
SE	0.52	0.41
95% CI	(-3.97, -1.92)	(-2.77, -1.15)
LS mean difference (tofersen - placebo)		1.0
SE		0.56
95% CI		(-0.11, 2.07)
p-value		0.0772
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.24, 0.79)
p-value		0.3014

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	21 (58.3)	51 (70.8)
Number of imputed values per imputation	15 (41.7)	21 (29.2)
LS mean change from baseline	-2.9	-2.1
SE	0.57	0.45
95% CI	(-3.99, -1.77)	(-3.02, -1.25)
LS mean difference (tofersen - placebo)		0.7
SE		0.61
95% CI		(-0.45, 1.94)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.33, 0.69)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Fine Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 104		
Number of observations per imputation	20 (55.6)	49 (68.1)
Number of imputed values per imputation	16 (44.4)	23 (31.9)
LS mean change from baseline	-3.5	-2.5
SE	0.60	0.47
95% CI	(-4.72, -2.37)	(-3.40, -1.57)
LS mean difference (tofersen - placebo)		1.1
SE		0.65
95% CI		(-0.21, 2.32)
p-value		0.1013
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.27, 0.78)
p-value		0.3405

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.7	-0.6
SE	0.24	0.19
95% CI	(-1.16, -0.23)	(-0.93, -0.19)
LS mean difference (tofersen - placebo)		0.1
SE		0.26
95% CI		(-0.38, 0.64)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.34, 0.47)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-2.0	-1.0
SE	0.33	0.26
95% CI	(-2.61, -1.31)	(-1.51, -0.49)
LS mean difference (tofersen - placebo)		1.0
SE		0.36
95% CI		(0.25, 1.67)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.01, 0.84)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.3	-1.3
SE	0.36	0.29
95% CI	(-3.01, -1.59)	(-1.86, -0.74)
LS mean difference (tofersen - placebo)		1.0
SE		0.40
95% CI		(0.22, 1.78)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.01, 0.89)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-2.1	-1.1
SE	0.39	0.30
95% CI	(-2.84, -1.33)	(-1.71, -0.52)
LS mean difference (tofersen - placebo)		1.0
SE		0.42
95% CI		(0.14, 1.79)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.06, 0.85)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	22 (61.1)	55 (76.4)
Number of imputed values per imputation	14 (38.9)	17 (23.6)
LS mean change from baseline	-2.1	-1.2
SE	0.37	0.29
95% CI	(-2.80, -1.33)	(-1.74, -0.59)
LS mean difference (tofersen - placebo)		0.9
SE		0.41
95% CI		(0.10, 1.70)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.12, 0.87)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	54 (75.0)
Number of imputed values per imputation	16 (44.4)	18 (25.0)
LS mean change from baseline	-2.3	-1.2
SE	0.40	0.31
95% CI	(-3.08, -1.52)	(-1.80, -0.58)
LS mean difference (tofersen - placebo)		1.1
SE		0.43
95% CI		(0.26, 1.96)
p-value		0.0103
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.07, 0.96)
p-value		0.0925

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	21 (58.3)	51 (70.8)
Number of imputed values per imputation	15 (41.7)	21 (29.2)
LS mean change from baseline	-2.5	-1.5
SE	0.41	0.32
95% CI	(-3.27, -1.67)	(-2.09, -0.84)
LS mean difference (tofersen - placebo)		1.0
SE		0.44
95% CI		(0.14, 1.87)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.11, 0.91)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Gross Motor Skill Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 104		
Number of observations per imputation	20 (55.6)	49 (68.1)
Number of imputed values per imputation	16 (44.4)	23 (31.9)
LS mean change from baseline	-3.1	-1.6
SE	0.46	0.36
95% CI	(-3.97, -2.18)	(-2.28, -0.87)
LS mean difference (tofersen - placebo)		1.5
SE		0.50
95% CI		(0.53, 2.48)
p-value		0.0025
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(0.02, 1.07)
p-value		0.0433

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	-0.5	-0.2
SE	0.35	0.27
95% CI	(-1.17, 0.18)	(-0.77, 0.29)
LS mean difference (tofersen - placebo)		0.3
SE		0.38
95% CI		(-0.49, 0.99)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.29, 0.52)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	33 (91.7)	63 (87.5)
Number of imputed values per imputation	3 (8.3)	9 (12.5)
LS mean change from baseline	-1.7	-1.3
SE	0.50	0.39
95% CI	(-2.69, -0.72)	(-2.11, -0.59)
LS mean difference (tofersen - placebo)		0.4
SE		0.55
95% CI		(-0.72, 1.43)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.37, 0.48)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	29 (80.6)	58 (80.6)
Number of imputed values per imputation	7 (19.4)	14 (19.4)
LS mean change from baseline	-2.8	-1.7
SE	0.60	0.47
95% CI	(-4.01, -1.66)	(-2.64, -0.80)
LS mean difference (tofersen - placebo)		1.1
SE		0.66
95% CI		(-0.17, 2.40)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.18, 0.72)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	28 (77.8)	57 (79.2)
Number of imputed values per imputation	8 (22.2)	15 (20.8)
LS mean change from baseline	-3.1	-1.9
SE	0.62	0.48
95% CI	(-4.34, -1.92)	(-2.84, -0.95)
LS mean difference (tofersen - placebo)		1.2
SE		0.67
95% CI		(-0.07, 2.55)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.18, 0.73)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	22 (61.1)	55 (76.4)
Number of imputed values per imputation	14 (38.9)	17 (23.6)
LS mean change from baseline	-3.4	-2.2
SE	0.62	0.49
95% CI	(-4.65, -2.21)	(-3.13, -1.22)
LS mean difference (tofersen - placebo)		1.3
SE		0.67
95% CI		(-0.06, 2.57)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.23, 0.77)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
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233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	54 (75.0)
Number of imputed values per imputation	16 (44.4)	18 (25.0)
LS mean change from baseline	-3.4	-2.3
SE	0.65	0.51
95% CI	(-4.66, -2.13)	(-3.27, -1.29)
LS mean difference (tofersen - placebo)		1.1
SE		0.69
95% CI		(-0.25, 2.47)
p-value		0.1099
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.28, 0.75)
p-value		0.3762

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	21 (58.3)	51 (70.8)
Number of imputed values per imputation	15 (41.7)	21 (29.2)
LS mean change from baseline	-3.7	-2.4
SE	0.70	0.54
95% CI	(-5.06, -2.32)	(-3.43, -1.31)
LS mean difference (tofersen - placebo)		1.3
SE		0.74
95% CI		(-0.13, 2.76)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.22, 0.80)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSFRS-R domain score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

ALSFRS-R Respiratory Domain Score

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 104		
Number of observations per imputation	20 (55.6)	49 (68.1)
Number of imputed values per imputation	16 (44.4)	23 (31.9)
LS mean change from baseline	-3.6	-2.8
SE	0.79	0.61
95% CI	(-5.14, -2.06)	(-3.99, -1.58)
LS mean difference (tofersen - placebo)		0.8
SE		0.79
95% CI		(-0.74, 2.37)
p-value		0.3026
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.38, 0.66)
p-value		0.6004

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Four domain scores include bulbar function (Q1-Q3), fine motor skills (Q4-Q6), gross motor skills (Q7-Q9), and respiratory function (Q10-Q12). A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSFRS-R domain score, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-alsf-dm-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in ALSFRS-R total score at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 76		
Average proportion of subjects with stabilization or improvement in ALSFRS-R total score	28.5	33.4
Adjusted RR - Relative Risk (tofersen/placebo)		1.26
SE of log(RR)		0.304
95% CI		(0.692, 2.278)
p-value		0.4535
Adjusted OR - Odds Ratio (tofersen/placebo)		1.43
SE of log(OR)		0.466
95% CI		(0.572, 3.553)
p-value		0.4466
ARR - Absolute Risk Reduction (tofersen - placebo)		0.05
SE of ARR		0.094
95% CI		(-0.136, 0.234)
p-value		0.6031

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-als-tot-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in ALSFRS-R total score at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 104		
Average proportion of subjects with stabilization or improvement in ALSFRS-R total score	22.7	29.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.37
SE of log(RR)		0.352
95% CI		(0.686, 2.732)
p-value		0.3722
Adjusted OR - Odds Ratio (tofersen/placebo)		1.55
SE of log(OR)		0.484
95% CI		(0.600, 4.005)
p-value		0.3648
ARR - Absolute Risk Reduction (tofersen - placebo)		0.07
SE of ARR		0.089
95% CI		(-0.109, 0.239)
p-value		0.4618

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-als-tot-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	35 (97.2)	64 (88.9)
Number of imputed values per imputation	1 (2.8)	8 (11.1)
LS mean change from baseline	-0.14	-0.11
SE	0.052	0.041
95% CI	(-0.238, -0.034)	(-0.188, -0.027)
LS mean difference (tofersen - placebo)		0.03
SE		0.057
95% CI		(-0.083, 0.139)
Hedge's g standardized mean difference (tofersen - placebo)		0.08
95% CI		(-0.327, 0.497)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	27 (75.0)	58 (80.6)
Number of imputed values per imputation	9 (25.0)	14 (19.4)
LS mean change from baseline	-0.29	-0.21
SE	0.061	0.046
95% CI	(-0.411, -0.171)	(-0.303, -0.121)
LS mean difference (tofersen - placebo)		0.08
SE		0.068
95% CI		(-0.054, 0.212)
Hedge's g standardized mean difference (tofersen - placebo)		0.20
95% CI		(-0.262, 0.653)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 40		
Number of observations per imputation	24 (66.7)	47 (65.3)
Number of imputed values per imputation	12 (33.3)	25 (34.7)
LS mean change from baseline	-0.43	-0.19
SE	0.082	0.062
95% CI	(-0.594, -0.273)	(-0.310, -0.066)
LS mean difference (tofersen - placebo)		0.25
SE		0.088
95% CI		(0.073, 0.419)
Hedge's g standardized mean difference (tofersen - placebo)		0.53
95% CI		(0.027, 1.026)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	25 (69.4)	42 (58.3)
Number of imputed values per imputation	11 (30.6)	30 (41.7)
LS mean change from baseline	-0.41	-0.16
SE	0.098	0.080
95% CI	(-0.606, -0.223)	(-0.313, 0.002)
LS mean difference (tofersen - placebo)		0.26
SE		0.106
95% CI		(0.051, 0.468)
Hedge's g standardized mean difference (tofersen - placebo)		0.51
95% CI		(0.009, 1.015)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	19 (52.8)	50 (69.4)
Number of imputed values per imputation	17 (47.2)	22 (30.6)
LS mean change from baseline	-0.43	-0.21
SE	0.105	0.077
95% CI	(-0.638, -0.227)	(-0.366, -0.064)
LS mean difference (tofersen - placebo)		0.22
SE		0.111
95% CI		(0.000, 0.436)
Hedge's g standardized mean difference (tofersen - placebo)		0.39
95% CI		(-0.141, 0.924)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	17 (47.2)	45 (62.5)
Number of imputed values per imputation	19 (52.8)	27 (37.5)
LS mean change from baseline	-0.44	-0.28
SE	0.119	0.081
95% CI	(-0.674, -0.204)	(-0.439, -0.120)
LS mean difference (tofersen - placebo)		0.16
SE		0.117
95% CI		(-0.071, 0.390)
p-value		0.1756
Hedge's g standardized mean difference (tofersen - placebo)		0.25
95% CI		(-0.307, 0.813)
p-value		0.3752

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	19 (52.8)	46 (63.9)
Number of imputed values per imputation	17 (47.2)	26 (36.1)
LS mean change from baseline	-0.48	-0.33
SE	0.137	0.095
95% CI	(-0.748, -0.209)	(-0.518, -0.143)
LS mean difference (tofersen - placebo)		0.15
SE		0.142
95% CI		(-0.131, 0.426)
Hedge's g standardized mean difference (tofersen - placebo)		0.22
95% CI		(-0.318, 0.753)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: HHD overall megascore change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 104		
Number of observations per imputation	10 (27.8)	32 (44.4)
Number of imputed values per imputation	26 (72.2)	40 (55.6)
LS mean change from baseline	-0.58	-0.39
SE	0.148	0.107
95% CI	(-0.874, -0.290)	(-0.604, -0.183)
LS mean difference (tofersen - placebo)		0.19
SE		0.145
95% CI		(-0.097, 0.474)
p-value		0.1946
Hedge's g standardized mean difference (tofersen - placebo)		0.26
95% CI		(-0.449, 0.976)
p-value		0.4689

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-ancmi-clitt.sas **Data Cutoff:** **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in HHD megascore at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 76		
Average proportion of subjects with stabilization or improvement in HHD megascore	13.8	33.0
Adjusted RR - Relative Risk (tofersen/placebo)		2.68
SE of log(RR)		0.487
95% CI		(1.034, 6.971)
p-value		0.0425
Adjusted OR - Odds Ratio (tofersen/placebo)		4.26
SE of log(OR)		0.681
95% CI		(1.119, 16.193)
p-value		0.0336
ARR - Absolute Risk Reduction (tofersen - placebo)		0.19
SE of ARR		0.086
95% CI		(0.023, 0.360)
p-value		0.0256

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in HHD megascore at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 104		
Average proportion of subjects with stabilization or improvement in HHD megascore	10.1	25.8
Adjusted RR - Relative Risk (tofersen/placebo)		2.97
SE of log(RR)		0.666
95% CI		(0.804, 10.981)
p-value		0.1023
Adjusted OR - Odds Ratio (tofersen/placebo)		4.09
SE of log(OR)		0.811
95% CI		(0.834, 20.082)
p-value		0.0825
ARR - Absolute Risk Reduction (tofersen - placebo)		0.16
SE of ARR		0.081
95% CI		(-0.002, 0.316)
p-value		0.0529

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The overall megascore calculated as an average normalized Z scores across the 16 muscles. A positive change indicates an improvement. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-mega-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	34 (94.4)	59 (81.9)
Number of imputed values per imputation	2 (5.6)	13 (18.1)
LS mean change from baseline	-6.9	-3.2
SE	1.78	1.38
95% CI	(-10.37, -3.40)	(-5.94, -0.52)
LS mean difference (tofersen - placebo)		3.6
SE		1.95
95% CI		(-0.18, 7.48)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.15, 0.69)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	25 (69.4)	52 (72.2)
Number of imputed values per imputation	11 (30.6)	20 (27.8)
LS mean change from baseline	-14.8	-6.8
SE	3.11	2.33
95% CI	(-20.94, -8.76)	(-11.38, -2.26)
LS mean difference (tofersen - placebo)		8.0
SE		3.34
95% CI		(1.49, 14.58)
Hedge's g standardized mean difference (tofersen - placebo)		0.4
95% CI		(-0.11, 0.85)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	20 (55.6)	39 (54.2)
Number of imputed values per imputation	16 (44.4)	33 (45.8)
LS mean change from baseline	-20.5	-9.1
SE	3.41	2.69
95% CI	(-27.16, -13.78)	(-14.39, -3.85)
LS mean difference (tofersen - placebo)		11.4
SE		3.72
95% CI		(4.06, 18.64)
Hedge's g standardized mean difference (tofersen - placebo)		0.5
95% CI		(-0.08, 1.01)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	20 (55.6)	38 (52.8)
Number of imputed values per imputation	16 (44.4)	34 (47.2)
LS mean change from baseline	-18.6	-10.4
SE	3.72	2.84
95% CI	(-25.86, -11.26)	(-15.95, -4.79)
LS mean difference (tofersen - placebo)		8.2
SE		3.91
95% CI		(0.53, 15.85)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.25, 0.84)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	17 (47.2)	41 (56.9)
Number of imputed values per imputation	19 (52.8)	31 (43.1)
LS mean change from baseline	-21.7	-12.3
SE	4.27	3.22
95% CI	(-30.05, -13.29)	(-18.68, -6.02)
LS mean difference (tofersen - placebo)		9.3
SE		4.21
95% CI		(1.07, 17.57)
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.25, 0.89)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	17 (47.2)	39 (54.2)
Number of imputed values per imputation	19 (52.8)	33 (45.8)
LS mean change from baseline	-20.4	-12.7
SE	4.52	3.60
95% CI	(-29.24, -11.50)	(-19.81, -5.67)
LS mean difference (tofersen - placebo)		7.6
SE		4.54
95% CI		(-1.27, 16.54)
p-value		0.0929
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.33, 0.81)
p-value		0.4081

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	15 (41.7)	40 (55.6)
Number of imputed values per imputation	21 (58.3)	32 (44.4)
LS mean change from baseline	-22.0	-14.1
SE	5.55	4.18
95% CI	(-32.85, -11.06)	(-22.32, -5.92)
LS mean difference (tofersen - placebo)		7.8
SE		5.46
95% CI		(-2.89, 18.55)
Hedge's g standardized mean difference (tofersen - placebo)		0.2
95% CI		(-0.38, 0.81)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Percent predicted SVC (percent) change from baseline by time point ANCOVA analysis using MI for pooled CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 104		
Number of observations per imputation	10 (27.8)	31 (43.1)
Number of imputed values per imputation	26 (72.2)	41 (56.9)
LS mean change from baseline	-24.2	-14.5
SE	6.08	4.49
95% CI	(-36.19, -12.25)	(-23.36, -5.66)
LS mean difference (tofersen - placebo)		9.7
SE		5.35
95% CI		(-0.80, 20.22)
p-value		0.0702
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.43, 1.00)
p-value		0.4302

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data. Readings with ATS Best criteria F (failed) are considered as missing and imputed using MI.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; ATS = the American Thoracic Society.
Source: biib067/valueaccess/amnog4/t-cf-svc-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in percent predicted SVC at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 76		
Average proportion of subjects with stabilization or improvement in percent predicted SVC	11.0	26.5
Adjusted RR - Relative Risk (tofersen/placebo)		2.56
SE of log(RR)		0.556
95% CI		(0.860, 7.600)
p-value		0.0913
Adjusted OR - Odds Ratio (tofersen/placebo)		3.08
SE of log(OR)		0.632
95% CI		(0.891, 10.625)
p-value		0.0754
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.079
95% CI		(-0.001, 0.310)
p-value		0.0517

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-svc-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in percent predicted SVC at Week 76 and 104 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 104		
Average proportion of subjects with stabilization or improvement in percent predicted SVC	10.5	21.4
Adjusted RR - Relative Risk (tofersen/placebo)		2.34
SE of log(RR)		0.652
95% CI		(0.652, 8.415)
p-value		0.1918
Adjusted OR - Odds Ratio (tofersen/placebo)		2.91
SE of log(OR)		0.786
95% CI		(0.621, 13.589)
p-value		0.1753
ARR - Absolute Risk Reduction (tofersen - placebo)		0.11
SE of ARR		0.082
95% CI		(-0.052, 0.269)
p-value		0.1835

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement. Subjects with no change or any increase compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with decrease compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; MI = multiple imputation.
Source: biib067/valueaccess/amnog4/t-cf-svc-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	35 (97.2)	66 (91.7)
Number of imputed values per imputation	1 (2.8)	6 (8.3)
LS mean change from baseline	1.6	0.2
SE	1.89	1.48
95% CI	(-2.07, 5.33)	(-2.69, 3.11)
LS mean difference (tofersen - placebo)		-1.4
SE		2.05
95% CI		(-5.45, 2.60)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.50, 0.32)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 28		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	6.4	3.9
SE	2.36	1.83
95% CI	(1.81, 11.07)	(0.33, 7.52)
LS mean difference (tofersen - placebo)		-2.5
SE		2.58
95% CI		(-7.57, 2.55)
Hedge's g standardized mean difference (tofersen - placebo)		-0.1
95% CI		(-0.57, 0.30)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 40		
Number of observations per imputation	28 (77.8)	50 (69.4)
Number of imputed values per imputation	8 (22.2)	22 (30.6)
LS mean change from baseline	2.7	3.9
SE	2.26	1.76
95% CI	(-1.70, 7.17)	(0.49, 7.41)
LS mean difference (tofersen - placebo)		1.2
SE		2.45
95% CI		(-3.58, 6.01)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.32, 0.61)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	26 (72.2)	49 (68.1)
Number of imputed values per imputation	10 (27.8)	23 (31.9)
LS mean change from baseline	5.1	1.5
SE	2.48	1.92
95% CI	(0.27, 10.02)	(-2.25, 5.27)
LS mean difference (tofersen - placebo)		-3.6
SE		2.65
95% CI		(-8.82, 1.55)
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.71, 0.24)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	23 (63.9)	50 (69.4)
Number of imputed values per imputation	13 (36.1)	22 (30.6)
LS mean change from baseline	3.4	2.3
SE	2.63	1.99
95% CI	(-1.79, 8.53)	(-1.57, 6.24)
LS mean difference (tofersen - placebo)		-1.0
SE		2.74
95% CI		(-6.40, 4.33)
Hedge's g standardized mean difference (tofersen - placebo)		0.0
95% CI		(-0.53, 0.45)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	47 (65.3)
Number of imputed values per imputation	16 (44.4)	25 (34.7)
LS mean change from baseline	1.0	4.0
SE	2.30	1.73
95% CI	(-3.47, 5.54)	(0.59, 7.39)
LS mean difference (tofersen - placebo)		3.0
SE		2.44
95% CI		(-1.83, 7.74)
p-value		0.2258
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.22, 0.83)
p-value		0.2607

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	19 (52.8)	44 (61.1)
Number of imputed values per imputation	17 (47.2)	28 (38.9)
LS mean change from baseline	4.1	4.7
SE	2.56	1.92
95% CI	(-0.96, 9.08)	(0.92, 8.47)
LS mean difference (tofersen - placebo)		0.6
SE		2.81
95% CI		(-4.88, 6.14)
Hedge's g standardized mean difference (tofersen - placebo)		0.1
95% CI		(-0.46, 0.62)

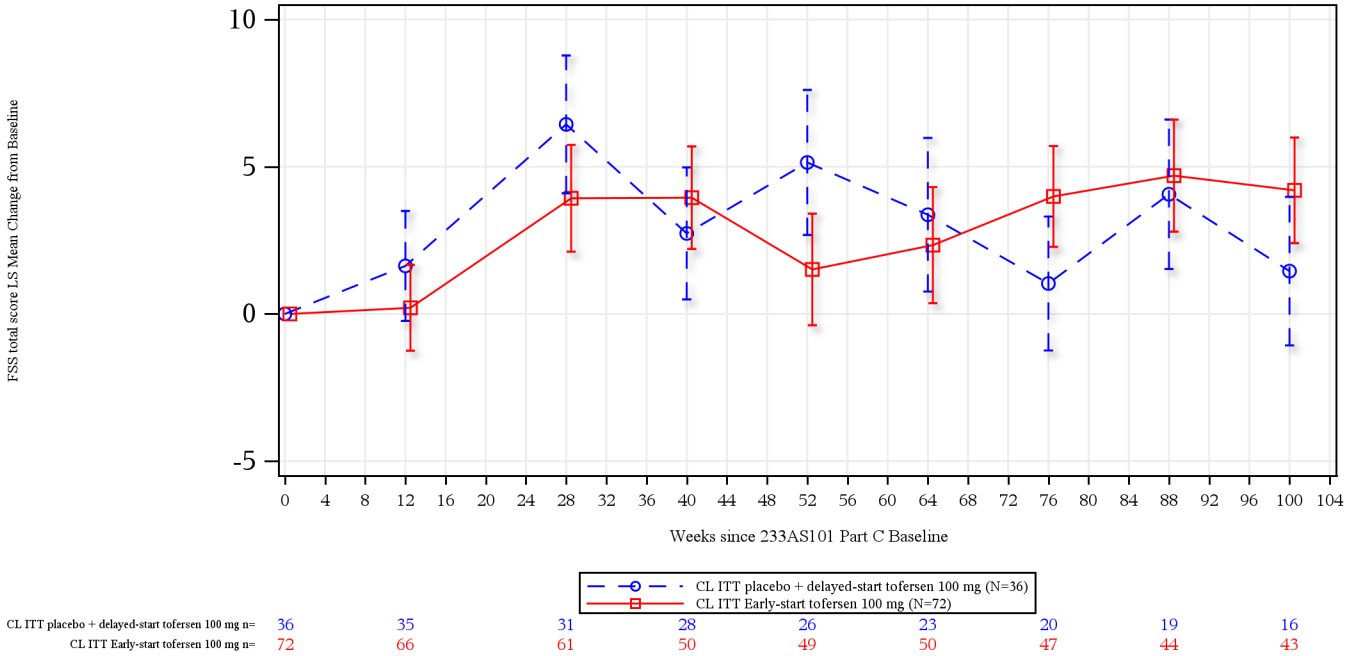
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: FSS total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 100		
Number of observations per imputation	16 (44.4)	43 (59.7)
Number of imputed values per imputation	20 (55.6)	29 (40.3)
LS mean change from baseline	1.5	4.2
SE	2.54	1.82
95% CI	(-3.54, 6.45)	(0.64, 7.76)
LS mean difference (tofersen - placebo)		2.7
SE		2.74
95% CI		(-2.64, 8.13)
p-value		0.3174
Hedge's g standardized mean difference (tofersen - placebo)		0.3
95% CI		(-0.30, 0.85)
p-value		0.3493

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-fss-ancmi-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: Line plot of FSS total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population



NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline FSS total score, and use of riluzole or edaravone.
Abbreviations: FSS = Fatigue Severity Scale; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla4/f-cf-fss-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 06JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in FSS total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Average proportion of subjects with stabilization or improvement in FSS total score	36.9	39.0
Adjusted RR - Relative Risk (tofersen/placebo)		1.13
SE of log(RR)		0.261
95% CI		(0.676, 1.882)
p-value		0.6440
Adjusted OR - Odds Ratio (tofersen/placebo)		1.24
SE of log(OR)		0.462
95% CI		(0.502, 3.074)
p-value		0.6382
ARR - Absolute Risk Reduction (tofersen - placebo)		0.02
SE of ARR		0.101
95% CI		(-0.178, 0.219)
p-value		0.8379

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life. Subjects with no change or any decrease compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog4/t-cf-fss-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in FSS total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 100		
Average proportion of subjects with stabilization or improvement in FSS total score	32.8	33.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.09
SE of log(RR)		0.295
95% CI		(0.613, 1.951)
p-value		0.7614
Adjusted OR - Odds Ratio (tofersen/placebo)		1.16
SE of log(OR)		0.475
95% CI		(0.456, 2.934)
p-value		0.7601
ARR - Absolute Risk Reduction (tofersen - placebo)		0.01
SE of ARR		0.100
95% CI		(-0.187, 0.203)
p-value		0.9377

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life. Subjects with no change or any decrease compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog4/t-cf-fss-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in FSS total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 76		
Average proportion of subjects with improvement in FSS total score	28.6	34.8
Adjusted RR - Relative Risk (tofersen/placebo)		1.32
SE of log(RR)		0.308
95% CI		(0.722, 2.410)
p-value		0.3682
Adjusted OR - Odds Ratio (tofersen/placebo)		1.58
SE of log(OR)		0.494
95% CI		(0.600, 4.161)
p-value		0.3544
ARR - Absolute Risk Reduction (tofersen - placebo)		0.06
SE of ARR		0.096
95% CI		(-0.126, 0.251)
p-value		0.5175

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life. Subjects with any decrease compared to 233AS101 baseline are classed as improvement responders, and subjects with no change or with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog4/t-cf-fss-respi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in FSS total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 100		
Average proportion of subjects with improvement in FSS total score	25.1	25.3
Adjusted RR - Relative Risk (tofersen/placebo)		1.08
SE of log(RR)		0.363
95% CI		(0.528, 2.197)
p-value		0.8372
Adjusted OR - Odds Ratio (tofersen/placebo)		1.11
SE of log(OR)		0.510
95% CI		(0.409, 3.018)
p-value		0.8360
ARR - Absolute Risk Reduction (tofersen - placebo)		0.00
SE of ARR		0.092
95% CI		(-0.179, 0.181)
p-value		0.9903

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates less fatigue in everyday life. Subjects with any decrease compared to 233AS101 baseline are classed as improvement responders, and subjects with no change or with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: FSS = Fatigue Severity Scale.
Source: biib067/valueaccess/amnog4/t-cf-fss-respi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Baseline		
Number of observations per imputation	36 (100)	72 (100)
Number of imputed values per imputation	0	0
Week 12		
Number of observations per imputation	[redacted]	
Number of imputed values per imputation		
LS mean change from baseline	6.0	2.1
SE	1.98	1.56
95% CI	(2.07, 9.83)	(-0.98, 5.12)
LS mean difference (tofersen - placebo)		-3.9
SE		2.17
95% CI		(-8.12, 0.37)
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.76, 0.06)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 28		
Number of observations per imputation	31 (86.1)	61 (84.7)
Number of imputed values per imputation	5 (13.9)	11 (15.3)
LS mean change from baseline	12.6	6.9
SE	2.88	2.23
95% CI	(6.99, 18.28)	(2.53, 11.26)
LS mean difference (tofersen - placebo)		-5.7
SE		3.18
95% CI		(-11.97, 0.49)
Hedge's g standardized mean difference (tofersen - placebo)		-0.3
95% CI		(-0.77, 0.10)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg	Early-start tofersen 100 mg
	(N=36)	(N=72)
Week 40		
Number of observations per imputation	28 (77.8)	50 (69.4)
Number of imputed values per imputation	8 (22.2)	22 (30.6)
LS mean change from baseline	15.8	7.6
SE	3.47	2.73
95% CI	(9.05, 22.64)	(2.29, 12.99)
LS mean difference (tofersen - placebo)		-8.2
SE		3.80
95% CI		(-15.66, -0.75)
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.87, 0.07)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 52		
Number of observations per imputation	26 (72.2)	49 (68.1)
Number of imputed values per imputation	10 (27.8)	23 (31.9)
LS mean change from baseline	20.0	9.2
SE	3.35	2.73
95% CI	(13.38, 26.53)	(3.81, 14.53)
LS mean difference (tofersen - placebo)		-10.8
SE		3.65
95% CI		(-17.95, -3.63)
Hedge's g standardized mean difference (tofersen - placebo)		-0.5
95% CI		(-0.96, 0.00)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 64		
Number of observations per imputation	23 (63.9)	48 (66.7)
Number of imputed values per imputation	13 (36.1)	24 (33.3)
LS mean change from baseline	17.9	9.7
SE	3.57	2.86
95% CI	(10.90, 24.92)	(4.04, 15.27)
LS mean difference (tofersen - placebo)		-8.3
SE		3.86
95% CI		(-15.82, -0.69)
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.89, 0.12)

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Number of observations per imputation	20 (55.6)	46 (63.9)
Number of imputed values per imputation	16 (44.4)	26 (36.1)
LS mean change from baseline	24.5	13.8
SE	4.30	3.29
95% CI	(16.02, 32.91)	(7.31, 20.24)
LS mean difference (tofersen - placebo)		-10.7
SE		4.58
95% CI		(-19.67, -1.70)
p-value		0.0198
Hedge's g standardized mean difference (tofersen - placebo)		-0.4
95% CI		(-0.93, 0.13)
p-value		0.1403

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 88		
Number of observations per imputation	19 (52.8)	44 (61.1)
Number of imputed values per imputation	17 (47.2)	28 (38.9)
LS mean change from baseline	22.9	15.7
SE	4.71	3.64
95% CI	(13.67, 32.15)	(8.58, 22.87)
LS mean difference (tofersen - placebo)		-7.2
SE		4.95
95% CI		(-16.90, 2.53)
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.78, 0.30)

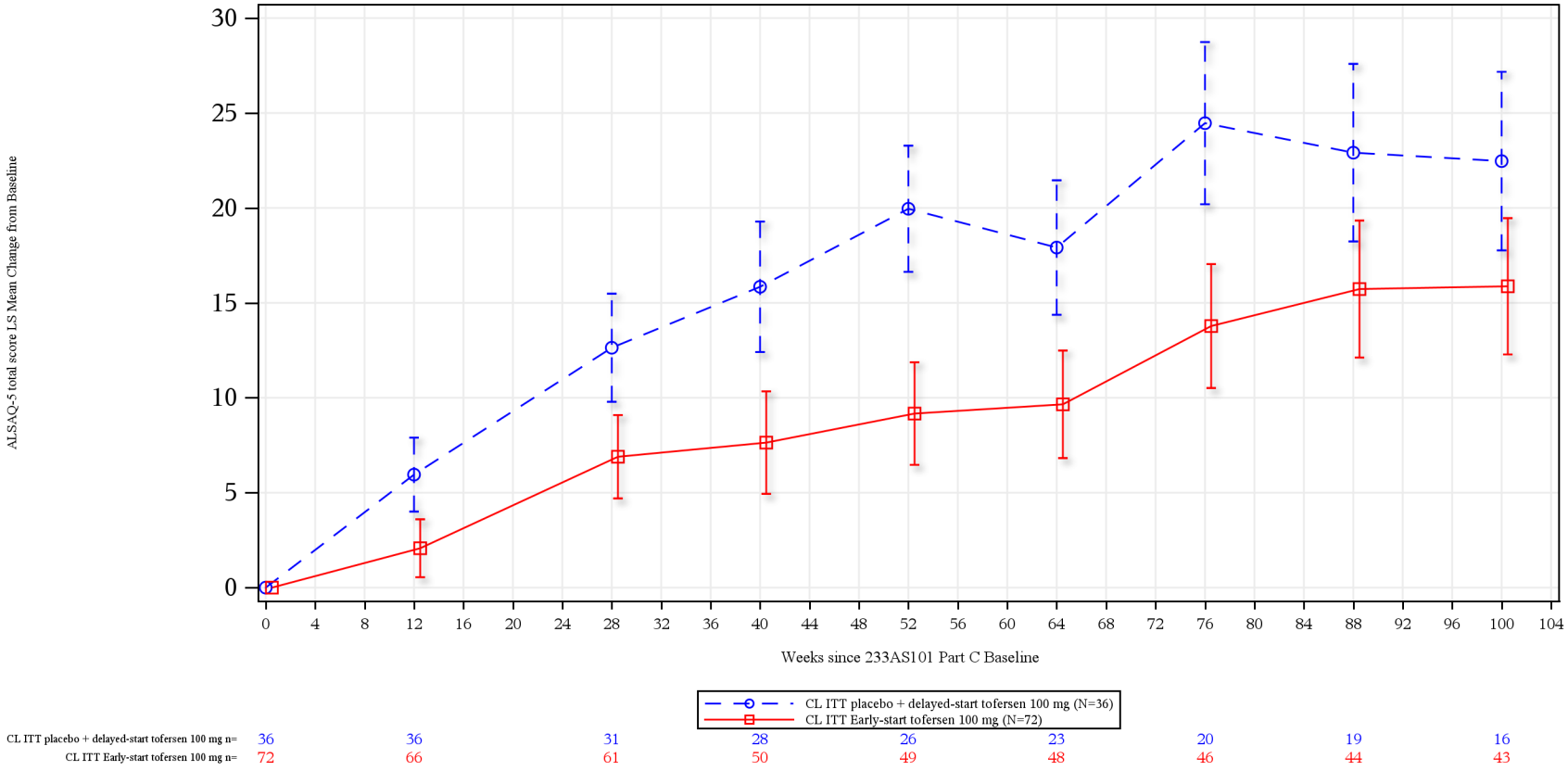
NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: ALSAQ-5 total score change from baseline by time point ANCOVA analysis using MI for pooled group CL - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	Placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 100		
Number of observations per imputation	16 (44.4)	43 (59.7)
Number of imputed values per imputation	20 (55.6)	29 (40.3)
LS mean change from baseline	22.5	15.9
SE	4.73	3.62
95% CI	(13.17, 31.76)	(8.77, 22.98)
LS mean difference (tofersen - placebo)		-6.6
SE		4.97
95% CI		(-16.34, 3.15)
p-value		0.1845
Hedge's g standardized mean difference (tofersen - placebo)		-0.2
95% CI		(-0.79, 0.36)
p-value		0.4703

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/valueaccess/amnog4/t-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISE: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population



CL ITT placebo + delayed-start tofersen 100 mg n=	36	36	31	28	26	23	20	19	16
CL ITT Early-start tofersen 100 mg n=	72	66	61	50	49	48	46	44	43

Footnotes are displayed on last page.

Source: biib067/ise/ise-bla4/f-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 05JUN2023

233AS101 and 233AS102 ISE: Line plot of ALSAQ-5 total score LS mean change from baseline values +/- SE by time point from ANCOVA analysis using MI for pooled group CL - ITT population

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including treatment group, use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates better health-related status.
NOTE 4: The ANCOVA model includes treatment as a fixed effect and adjusts for the following covariates: baseline plasma NfL, baseline ALSAQ-5 total score, and use of riluzole or edaravone.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.
Source: biib067/ise/ise-bla4/f-cf-aq5-anc-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 05JUN2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in ALSAQ-5 total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Average proportion of subjects with stabilization or improvement in ALSAQ-5 total score	11.7	38.1
Adjusted RR - Relative Risk (tofersen/placebo)		3.56
SE of log(RR)		0.492
95% CI		(1.357, 9.327)
p-value		0.0099
Adjusted OR - Odds Ratio (tofersen/placebo)		6.33
SE of log(OR)		0.645
95% CI		(1.789, 22.411)
p-value		0.0042
ARR - Absolute Risk Reduction (tofersen - placebo)		0.26
SE of ARR		0.081
95% CI		(0.104, 0.423)
p-value		0.0012

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates a better health-related status. Subjects with no change or any decrease compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog4/t-cf-aq5-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of stabilization or improvement in ALSAQ-5 total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Week 100		
Average proportion of subjects with stabilization or improvement in ALSAQ-5 total score	25.1	33.6
Adjusted RR - Relative Risk (tofersen/placebo)		1.46
SE of log(RR)		0.350
95% CI		(0.735, 2.901)
p-value		0.2793
Adjusted OR - Odds Ratio (tofersen/placebo)		1.82
SE of log(OR)		0.533
95% CI		(0.641, 5.189)
p-value		0.2596
ARR - Absolute Risk Reduction (tofersen - placebo)		0.08
SE of ARR		0.098
95% CI		(-0.107, 0.276)
p-value		0.3858

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates a better health-related status. Subjects with no change or any decrease compared to 233AS101 baseline are classed as stabilization or improvement responders, and subjects with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog4/t-cf-aq5-respsi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 76		
Average proportion of subjects with improvement in ALSAQ-5 total score	8.3	22.9
Adjusted RR - Relative Risk (tofersen/placebo)		2.99
SE of log(RR)		0.603
95% CI		(0.916, 9.745)
p-value		0.0695
Adjusted OR - Odds Ratio (tofersen/placebo)		3.90
SE of log(OR)		0.711
95% CI		(0.969, 15.727)
p-value		0.0555
ARR - Absolute Risk Reduction (tofersen - placebo)		0.15
SE of ARR		0.070
95% CI		(0.007, 0.283)
p-value		0.0393

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates a better health-related status. Subjects with any decrease compared to 233AS101 baseline are classed as improvement responders, and subjects with no change or with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog4/t-cf-aq5-respi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISE: Summary of proportion of improvement in ALSAQ-5 total score at Week 76 and 100 using MI - ITT population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	Early-start tofersen 100 mg (N=72)
Week 100		
Average proportion of subjects with improvement in ALSAQ-5 total score	16.1	19.7
Adjusted RR - Relative Risk (tofersen/placebo)		1.36
SE of log(RR)		0.502
95% CI		(0.508, 3.633)
p-value		0.5414
Adjusted OR - Odds Ratio (tofersen/placebo)		1.49
SE of log(OR)		0.639
95% CI		(0.425, 5.208)
p-value		0.5336
ARR - Absolute Risk Reduction (tofersen - placebo)		0.04
SE of ARR		0.085
95% CI		(-0.130, 0.202)
p-value		0.6694

NOTE 1: Baseline is defined as day 1 value prior to the study drug. If day 1 value is missing, the non-missing value (including screening visit) closest to and prior to the first dose will be used as the baseline value.
NOTE 2: Multiple imputation including use of riluzole or edaravone, baseline plasma NfL, and the relevant baseline and postbaseline values for the endpoint is used for missing data.
NOTE 3: A negative change indicates a better health-related status. Subjects with any decrease compared to 233AS101 baseline are classed as improvement responders, and subjects with no change or with increase compared to 233AS101 baseline are classed as non-responders. Any subjects who withdrew or died prior to the analysis visit are also classed as non-responders for the corresponding visit.
NOTE 4: Cochran-Mantel-Haenszel adjusted OR and RR are calculated adjusting for baseline plasma NfL, stratified by median NfL.
Abbreviations: ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
Source: biib067/valueaccess/amnog4/t-cf-aq5-respi.sas **Data Cutoff:** 28FEB2023 **Run Date:** 20JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	35 (97.2)	72 (100)
RR - Relative Risk (tofersen/placebo)		1.04
SE of log (RR)		0.035
95% CI		(0.966, 1.109)
p-value		0.3264
OR - Odds Ratio (tofersen/placebo)		6.13
SE of log (OR)		1.646
95% CI		(0.243, 154.217)
p-value		0.2707
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.034
95% CI		(-0.033, 0.100)
p-value		0.3193

Source: biib067/valueaccess/amnog4/t-ae-event-clitt.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Musculoskeletal and connective tissue disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	28 (77.8)	59 (81.9)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.105
95% CI		(0.858, 1.294)
p-value		0.6187
OR - Odds Ratio (tofersen/placebo)		1.30
SE of log (OR)		0.505
95% CI		(0.482, 3.486)
p-value		0.6066
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.083
95% CI		(-0.121, 0.204)
p-value		0.6148

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Injury, poisoning and procedural complications

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	33 (91.7)	58 (80.6)
RR - Relative Risk (tofersen/placebo)		0.88
SE of log (RR)		0.077
95% CI		(0.756, 1.021)
p-value		0.0919
OR - Odds Ratio (tofersen/placebo)		0.38
SE of log (OR)		0.673
95% CI		(0.101, 1.407)
p-value		0.1465
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.066
95% CI		(-0.240, 0.017)
p-value		0.0901

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Nervous system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	31 (86.1)	57 (79.2)
RR - Relative Risk (tofersen/placebo)		0.92
SE of log (RR)		0.090
95% CI		(0.770, 1.097)
p-value		0.3512
OR - Odds Ratio (tofersen/placebo)		0.61
SE of log (OR)		0.563
95% CI		(0.203, 1.846)
p-value		0.3842
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.075
95% CI		(-0.216, 0.077)
p-value		0.3540

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Infections and infestations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	27 (75.0)	51 (70.8)
RR - Relative Risk (tofersen/placebo)		0.94
SE of log (RR)		0.122
95% CI		(0.743, 1.200)
p-value		0.6405
OR - Odds Ratio (tofersen/placebo)		0.81
SE of log (OR)		0.464
95% CI		(0.326, 2.010)
p-value		0.6489
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.090
95% CI		(-0.218, 0.134)
p-value		0.6429

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Gastrointestinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	27 (75.0)	47 (65.3)
RR - Relative Risk (tofersen/placebo)		0.87
SE of log (RR)		0.129
95% CI		(0.676, 1.121)
p-value		0.2819
OR - Odds Ratio (tofersen/placebo)		0.63
SE of log (OR)		0.458
95% CI		(0.256, 1.537)
p-value		0.3072
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.091
95% CI		(-0.276, 0.082)
p-value		0.2875

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	22 (61.1)	43 (59.7)
RR - Relative Risk (tofersen/placebo)		0.98
SE of log (RR)		0.164
95% CI		(0.708, 1.349)
p-value		0.8888
OR - Odds Ratio (tofersen/placebo)		0.94
SE of log (OR)		0.418
95% CI		(0.416, 2.140)
p-value		0.8895
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.100
95% CI		(-0.209, 0.182)
p-value		0.8892

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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General disorders and administration site conditions

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	23 (63.9)	42 (58.3)
RR - Relative Risk (tofersen/placebo)		0.91
SE of log (RR)		0.160
95% CI		(0.667, 1.250)
p-value		0.5698
OR - Odds Ratio (tofersen/placebo)		0.79
SE of log (OR)		0.421
95% CI		(0.346, 1.807)
p-value		0.5785
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.099
95% CI		(-0.249, 0.138)
p-value		0.5744

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Investigations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	14 (38.9)	41 (56.9)
RR - Relative Risk (tofersen/placebo)		1.46
SE of log (RR)		0.233
95% CI		(0.928, 2.310)
p-value		0.1012
OR - Odds Ratio (tofersen/placebo)		2.08
SE of log (OR)		0.417
95% CI		(0.919, 4.702)
p-value		0.0791
ARR - Absolute Risk Reduction (tofersen/placebo)		0.18
SE of ARR		0.100
95% CI		(-0.016, 0.377)
p-value		0.0711

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Psychiatric disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	12 (33.3)	23 (31.9)
RR - Relative Risk (tofersen/placebo)		0.96
SE of log (RR)		0.292
95% CI		(0.541, 1.698)
p-value		0.8840
OR - Odds Ratio (tofersen/placebo)		0.94
SE of log (OR)		0.435
95% CI		(0.401, 2.200)
p-value		0.8844
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.096
95% CI		(-0.202, 0.174)
p-value		0.8848

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Skin and subcutaneous tissue disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	23 (31.9)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.305
95% CI		(0.576, 1.899)
p-value		0.8839
OR - Odds Ratio (tofersen/placebo)		1.07
SE of log (OR)		0.441
95% CI		(0.449, 2.534)
p-value		0.8835
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.094
95% CI		(-0.171, 0.199)
p-value		0.8830

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Renal and urinary disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		1.70
SE of log (RR)		0.466
95% CI		(0.682, 4.237)
p-value		0.2548
OR - Odds Ratio (tofersen/placebo)		1.92
SE of log (OR)		0.556
95% CI		(0.644, 5.700)
p-value		0.2422
ARR - Absolute Risk Reduction (tofersen/placebo)		0.10
SE of ARR		0.076
95% CI		(-0.052, 0.247)
p-value		0.2028

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Metabolism and nutrition disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	12 (33.3)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.54
SE of log (RR)		0.344
95% CI		(0.276, 1.064)
p-value		0.0750
OR - Odds Ratio (tofersen/placebo)		0.44
SE of log (OR)		0.468
95% CI		(0.176, 1.102)
p-value		0.0799
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.15
SE of ARR		0.091
95% CI		(-0.331, 0.025)
p-value		0.0921

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Eye disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	9 (25.0)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		0.56
SE of log (RR)		0.412
95% CI		(0.248, 1.245)
p-value		0.1533
OR - Odds Ratio (tofersen/placebo)		0.48
SE of log (OR)		0.514
95% CI		(0.177, 1.325)
p-value		0.1579
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.083
95% CI		(-0.274, 0.051)
p-value		0.1801

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Cardiac disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.80
SE of log (RR)		0.532
95% CI		(0.282, 2.271)
p-value		0.6751
OR - Odds Ratio (tofersen/placebo)		0.78
SE of log (OR)		0.611
95% CI		(0.234, 2.565)
p-value		0.6764
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.069
95% CI		(-0.162, 0.107)
p-value		0.6852

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Vascular disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.80
SE of log (RR)		0.532
95% CI		(0.282, 2.271)
p-value		0.6751
OR - Odds Ratio (tofersen/placebo)		0.78
SE of log (OR)		0.611
95% CI		(0.234, 2.565)
p-value		0.6764
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.069
95% CI		(-0.162, 0.107)
p-value		0.6852

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by system organ class - safety population

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Immune system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.88
SE of log (RR)		0.593
95% CI		(0.274, 2.795)
p-value		0.8217
OR - Odds Ratio (tofersen/placebo)		0.86
SE of log (OR)		0.663
95% CI		(0.235, 3.159)
p-value		0.8221
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.063
95% CI		(-0.137, 0.109)
p-value		0.8254

NOTE 1: Include system organ class with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Procedural pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	26 (72.2)	46 (63.9)
RR - Relative Risk (tofersen/placebo)		0.88
SE of log (RR)		0.136
95% CI		(0.677, 1.155)
p-value		0.3678
OR - Odds Ratio (tofersen/placebo)		0.68
SE of log (OR)		0.446
95% CI		(0.284, 1.630)
p-value		0.3877
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.08
SE of ARR		0.094
95% CI		(-0.267, 0.100)
p-value		0.3737

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Nervous system disorders/Headache

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	22 (61.1)	46 (63.9)
RR - Relative Risk (tofersen/placebo)		1.05
SE of log (RR)		0.160
95% CI		(0.764, 1.430)
p-value		0.7808
OR - Odds Ratio (tofersen/placebo)		1.13
SE of log (OR)		0.421
95% CI		(0.494, 2.569)
p-value		0.7781
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.099
95% CI		(-0.166, 0.222)
p-value		0.7791

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Back pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	14 (38.9)	31 (43.1)
RR - Relative Risk (tofersen/placebo)		1.11
SE of log (RR)		0.249
95% CI		(0.680, 1.804)
p-value		0.6828
OR - Odds Ratio (tofersen/placebo)		1.19
SE of log (OR)		0.417
95% CI		(0.525, 2.688)
p-value		0.6790
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.100
95% CI		(-0.154, 0.238)
p-value		0.6770

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Pain in extremity

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	15 (41.7)	29 (40.3)
RR - Relative Risk (tofersen/placebo)		0.97
SE of log (RR)		0.244
95% CI		(0.599, 1.559)
p-value		0.8894
OR - Odds Ratio (tofersen/placebo)		0.94
SE of log (OR)		0.415
95% CI		(0.419, 2.129)
p-value		0.8899
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.100
95% CI		(-0.211, 0.183)
p-value		0.8900

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Fall

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	25 (69.4)	27 (37.5)
RR - Relative Risk (tofersen/placebo)		0.54
SE of log (RR)		0.188
95% CI		(0.374, 0.781)
p-value		0.0011
OR - Odds Ratio (tofersen/placebo)		0.26
SE of log (OR)		0.436
95% CI		(0.112, 0.621)
p-value		0.0023
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.32
SE of ARR		0.096
95% CI		(-0.507, -0.132)
p-value		0.0008

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/COVID-19

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	26 (36.1)
RR - Relative Risk (tofersen/placebo)		1.63
SE of log (RR)		0.349
95% CI		(0.820, 3.220)
p-value		0.1642
OR - Odds Ratio (tofersen/placebo)		1.98
SE of log (OR)		0.470
95% CI		(0.787, 4.970)
p-value		0.1466
ARR - Absolute Risk Reduction (tofersen/placebo)		0.14
SE of ARR		0.089
95% CI		(-0.036, 0.314)
p-value		0.1206

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Arthralgia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	12 (33.3)	24 (33.3)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.289
95% CI		(0.568, 1.761)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.433
95% CI		(0.428, 2.337)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.096
95% CI		(-0.189, 0.189)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Investigations/CSF protein increased

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	21 (29.2)
RR - Relative Risk (tofersen/placebo)		1.31
SE of log (RR)		0.362
95% CI		(0.646, 2.668)
p-value		0.4524
OR - Odds Ratio (tofersen/placebo)		1.44
SE of log (OR)		0.477
95% CI		(0.565, 3.674)
p-value		0.4440
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.088
95% CI		(-0.102, 0.241)
p-value		0.4278

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Fatigue

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	11 (30.6)	20 (27.8)
RR - Relative Risk (tofersen/placebo)		0.91
SE of log (RR)		0.315
95% CI		(0.490, 1.686)
p-value		0.7622
OR - Odds Ratio (tofersen/placebo)		0.87
SE of log (OR)		0.447
95% CI		(0.364, 2.101)
p-value		0.7636
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.093
95% CI		(-0.210, 0.155)
p-value		0.7656

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Investigations/CSF white blood cell count increased

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	20 (27.8)
RR - Relative Risk (tofersen/placebo)		5.00
SE of log (RR)		0.713
95% CI		(1.236, 20.223)
p-value		0.0240
OR - Odds Ratio (tofersen/placebo)		6.54
SE of log (OR)		0.774
95% CI		(1.435, 29.790)
p-value		0.0152
ARR - Absolute Risk Reduction (tofersen/placebo)		0.22
SE of ARR		0.065
95% CI		(0.095, 0.350)
p-value		0.0006

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post lumbar puncture syndrome

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	15 (41.7)	19 (26.4)
RR - Relative Risk (tofersen/placebo)		0.63
SE of log (RR)		0.279
95% CI		(0.367, 1.093)
p-value		0.1011
OR - Odds Ratio (tofersen/placebo)		0.50
SE of log (OR)		0.431
95% CI		(0.216, 1.168)
p-value		0.1097
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.15
SE of ARR		0.097
95% CI		(-0.343, 0.038)
p-value		0.1160

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Myalgia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		2.25
SE of log (RR)		0.514
95% CI		(0.822, 6.158)
p-value		0.1144
OR - Odds Ratio (tofersen/placebo)		2.67
SE of log (OR)		0.596
95% CI		(0.829, 8.578)
p-value		0.0999
ARR - Absolute Risk Reduction (tofersen/placebo)		0.14
SE of ARR		0.073
95% CI		(-0.004, 0.282)
p-value		0.0575

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Nausea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	9 (25.0)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		0.94
SE of log (RR)		0.358
95% CI		(0.468, 1.906)
p-value		0.8732
OR - Odds Ratio (tofersen/placebo)		0.93
SE of log (OR)		0.475
95% CI		(0.366, 2.350)
p-value		0.8736
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.088
95% CI		(-0.186, 0.158)
p-value		0.8743

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Muscle spasms

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	15 (20.8)
RR - Relative Risk (tofersen/placebo)		1.07
SE of log (RR)		0.410
95% CI		(0.480, 2.392)
p-value		0.8663
OR - Odds Ratio (tofersen/placebo)		1.09
SE of log (OR)		0.511
95% CI		(0.400, 2.971)
p-value		0.8659
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.081
95% CI		(-0.146, 0.174)
p-value		0.8647

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Constipation

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	12 (33.3)	14 (19.4)
RR - Relative Risk (tofersen/placebo)		0.58
SE of log (RR)		0.336
95% CI		(0.302, 1.128)
p-value		0.1090
OR - Odds Ratio (tofersen/placebo)		0.48
SE of log (OR)		0.462
95% CI		(0.195, 1.195)
p-value		0.1152
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.14
SE of ARR		0.091
95% CI		(-0.318, 0.040)
p-value		0.1285

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Salivary hypersecretion

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	14 (19.4)
RR - Relative Risk (tofersen/placebo)		3.50
SE of log (RR)		0.728
95% CI		(0.840, 14.575)
p-value		0.0852
OR - Odds Ratio (tofersen/placebo)		4.10
SE of log (OR)		0.786
95% CI		(0.879, 19.158)
p-value		0.0725
ARR - Absolute Risk Reduction (tofersen/placebo)		0.14
SE of ARR		0.060
95% CI		(0.021, 0.257)
p-value		0.0212

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	14 (19.4)
RR - Relative Risk (tofersen/placebo)		0.88
SE of log (RR)		0.393
95% CI		(0.405, 1.892)
p-value		0.7343
OR - Odds Ratio (tofersen/placebo)		0.84
SE of log (OR)		0.499
95% CI		(0.317, 2.248)
p-value		0.7356
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.084
95% CI		(-0.191, 0.136)
p-value		0.7395

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Dizziness

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.81
SE of log (RR)		0.400
95% CI		(0.371, 1.781)
p-value		0.6040
OR - Odds Ratio (tofersen/placebo)		0.77
SE of log (OR)		0.505
95% CI		(0.287, 2.073)
p-value		0.6066
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.083
95% CI		(-0.204, 0.121)
p-value		0.6148

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Pyrexia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		0.75
SE of log (RR)		0.408
95% CI		(0.337, 1.669)
p-value		0.4810
OR - Odds Ratio (tofersen/placebo)		0.70
SE of log (OR)		0.511
95% CI		(0.257, 1.904)
p-value		0.4848
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.082
95% CI		(-0.216, 0.105)
p-value		0.4983

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Muscular weakness

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	12 (16.7)
RR - Relative Risk (tofersen/placebo)		0.86
SE of log (RR)		0.430
95% CI		(0.369, 1.989)
p-value		0.7197
OR - Odds Ratio (tofersen/placebo)		0.83
SE of log (OR)		0.527
95% CI		(0.295, 2.326)
p-value		0.7210
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.079
95% CI		(-0.183, 0.128)
p-value		0.7259

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Paraesthesia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	11 (15.3)
RR - Relative Risk (tofersen/placebo)		0.69
SE of log (RR)		0.417
95% CI		(0.303, 1.558)
p-value		0.3694
OR - Odds Ratio (tofersen/placebo)		0.63
SE of log (OR)		0.518
95% CI		(0.229, 1.741)
p-value		0.3740
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.081
95% CI		(-0.229, 0.090)
p-value		0.3926

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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General disorders and administration site conditions/Pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		0.747
95% CI		(0.578, 10.814)
p-value		0.2201
OR - Odds Ratio (tofersen/placebo)		2.74
SE of log (OR)		0.803
95% CI		(0.568, 13.242)
p-value		0.2093
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.056
95% CI		(-0.026, 0.193)
p-value		0.1356

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Upper respiratory tract infection

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		2.50
SE of log (RR)		0.747
95% CI		(0.578, 10.814)
p-value		0.2201
OR - Odds Ratio (tofersen/placebo)		2.74
SE of log (OR)		0.803
95% CI		(0.568, 13.242)
p-value		0.2093
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.056
95% CI		(-0.026, 0.193)
p-value		0.1356

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.474
95% CI		(0.329, 2.111)
p-value		0.7007
OR - Odds Ratio (tofersen/placebo)		0.81
SE of log (OR)		0.562
95% CI		(0.268, 2.428)
p-value		0.7020
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.074
95% CI		(-0.173, 0.118)
p-value		0.7085

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	9 (12.5)
RR - Relative Risk (tofersen/placebo)		1.13
SE of log (RR)		0.565
95% CI		(0.372, 3.406)
p-value		0.8349
OR - Odds Ratio (tofersen/placebo)		1.14
SE of log (OR)		0.639
95% CI		(0.327, 3.998)
p-value		0.8345
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.065
95% CI		(-0.114, 0.142)
p-value		0.8315

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Dysphagia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	1 (2.8)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		4.00
SE of log (RR)		1.041
95% CI		(0.520, 30.762)
p-value		0.1829
OR - Odds Ratio (tofersen/placebo)		4.38
SE of log (OR)		1.081
95% CI		(0.526, 36.423)
p-value		0.1723
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.046
95% CI		(-0.007, 0.174)
p-value		0.0704

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Nasopharyngitis

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	9 (25.0)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.44
SE of log (RR)		0.441
95% CI		(0.187, 1.055)
p-value		0.0659
OR - Odds Ratio (tofersen/placebo)		0.38
SE of log (OR)		0.537
95% CI		(0.131, 1.075)
p-value		0.0680
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.14
SE of ARR		0.081
95% CI		(-0.298, 0.020)
p-value		0.0869

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Contusion

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.456
95% CI		(0.204, 1.223)
p-value		0.1289
OR - Odds Ratio (tofersen/placebo)		0.44
SE of log (OR)		0.549
95% CI		(0.149, 1.283)
p-value		0.1321
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.079
95% CI		(-0.265, 0.043)
p-value		0.1573

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Nervous system disorders/Pleocytosis

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.645
95% CI		(0.376, 4.725)
p-value		0.6558
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.710
95% CI		(0.342, 5.530)
p-value		0.6538
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.059
95% CI		(-0.088, 0.144)
p-value		0.6384

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Psychiatric disorders/Anxiety

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.577
95% CI		(0.323, 3.101)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.650
95% CI		(0.280, 3.572)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.064
95% CI		(-0.126, 0.126)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Psychiatric disorders/Insomnia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.577
95% CI		(0.323, 3.101)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.650
95% CI		(0.280, 3.572)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.064
95% CI		(-0.126, 0.126)
p-value		1.0000

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Cough

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.645
95% CI		(0.376, 4.725)
p-value		0.6558
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.710
95% CI		(0.342, 5.530)
p-value		0.6538
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.059
95% CI		(-0.088, 0.144)
p-value		0.6384

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Urinary tract infection

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.494
95% CI		(0.190, 1.317)
p-value		0.1606
OR - Odds Ratio (tofersen/placebo)		0.45
SE of log (OR)		0.579
95% CI		(0.143, 1.389)
p-value		0.1635
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.075
95% CI		(-0.243, 0.049)
p-value		0.1927

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Neck pain

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.58
SE of log (RR)		0.518
95% CI		(0.212, 1.609)
p-value		0.2977
OR - Odds Ratio (tofersen/placebo)		0.54
SE of log (OR)		0.599
95% CI		(0.167, 1.740)
p-value		0.3010
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.071
95% CI		(-0.209, 0.070)
p-value		0.3298

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Musculoskeletal and connective tissue disorders/Joint swelling

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.599
95% CI		(0.155, 1.616)
p-value		0.2469
OR - Odds Ratio (tofersen/placebo)		0.46
SE of log (OR)		0.669
95% CI		(0.125, 1.716)
p-value		0.2491
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.065
95% CI		(-0.197, 0.058)
p-value		0.2850

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Diarrhoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	13 (36.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.15
SE of log (RR)		0.534
95% CI		(0.054, 0.438)
p-value		0.0005
OR - Odds Ratio (tofersen/placebo)		0.10
SE of log (OR)		0.621
95% CI		(0.031, 0.351)
p-value		0.0003
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.31
SE of ARR		0.084
95% CI		(-0.471, -0.140)
p-value		0.0003

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Metabolism and nutrition disorders/Decreased appetite

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		0.50
SE of log (RR)		0.677
95% CI		(0.133, 1.885)
p-value		0.3059
OR - Odds Ratio (tofersen/placebo)		0.47
SE of log (OR)		0.739
95% CI		(0.111, 2.003)
p-value		0.3077
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.059
95% CI		(-0.171, 0.060)
p-value		0.3458

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Gastrointestinal disorders/Abdominal distension

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

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Injury, poisoning and procedural complications/Post procedural complication

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.38
SE of log (RR)		0.736
95% CI		(0.089, 1.587)
p-value		0.1826
OR - Odds Ratio (tofersen/placebo)		0.35
SE of log (OR)		0.793
95% CI		(0.073, 1.646)
p-value		0.1830
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.057
95% CI		(-0.182, 0.043)
p-value		0.2266

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Nervous system disorders/Hypoaesthesia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	5 (13.9)	3 (4.2)
RR - Relative Risk (tofersen/placebo)		0.30
SE of log (RR)		0.701
95% CI		(0.076, 1.186)
p-value		0.0860
OR - Odds Ratio (tofersen/placebo)		0.27
SE of log (OR)		0.762
95% CI		(0.061, 1.199)
p-value		0.0852
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.062
95% CI		(-0.219, 0.025)
p-value		0.1184

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event by preferred term - safety population

Injury, poisoning and procedural complications/Skin laceration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	4 (11.1)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.13
SE of log (RR)		1.099
95% CI		(0.014, 1.078)
p-value		0.0585
OR - Odds Ratio (tofersen/placebo)		0.11
SE of log (OR)		1.138
95% CI		(0.012, 1.049)
p-value		0.0551
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.10
SE of ARR		0.054
95% CI		(-0.203, 0.009)
p-value		0.0727

NOTE 1: Include preferred term with >=10% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-pt-event-cl.sas **Data Cutoff:** 28feb2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 1	7 (19.4)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		0.43
SE of log (RR)		0.518
95% CI		(0.155, 1.182)
p-value		0.1016
OR - Odds Ratio (tofersen/placebo)		0.38
SE of log (OR)		0.599
95% CI		(0.116, 1.219)
p-value		0.1032
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.11
SE of ARR		0.074
95% CI		(-0.255, 0.033)
p-value		0.1310

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-maxctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 2	13 (36.1)	31 (43.1)
RR - Relative Risk (tofersen/placebo)		1.19
SE of log (RR)		0.260
95% CI		(0.716, 1.984)
p-value		0.4984
OR - Odds Ratio (tofersen/placebo)		1.34
SE of log (OR)		0.421
95% CI		(0.586, 3.052)
p-value		0.4893
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.099
95% CI		(-0.125, 0.264)
p-value		0.4833

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-maxctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 3	8 (22.2)	19 (26.4)
RR - Relative Risk (tofersen/placebo)		1.19
SE of log (RR)		0.369
95% CI		(0.576, 2.446)
p-value		0.6412
OR - Odds Ratio (tofersen/placebo)		1.25
SE of log (OR)		0.482
95% CI		(0.488, 3.226)
p-value		0.6377
ARR - Absolute Risk Reduction (tofersen/placebo)		0.04
SE of ARR		0.087
95% CI		(-0.128, 0.211)
p-value		0.6304

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-maxctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 4	[redacted]	
RR - Relative Risk (tofersen/placebo)		5.58
SE of log (RR)		1.463
95% CI		(0.317, 98.127)
p-value		0.2403
OR - Odds Ratio (tofersen/placebo)		5.95
SE of log (OR)		1.491
95% CI		(0.320, 110.610)
p-value		0.2318
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.036
95% CI		(-0.009, 0.133)
p-value		0.0881

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-maxctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with adverse event by maximum CTCAE grade - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with events at maximum CTCAE grade 5	7 (19.4)	11 (15.3)
RR - Relative Risk (tofersen/placebo)		0.79
SE of log (RR)		0.438
95% CI		(0.333, 1.855)
p-value		0.5822
OR - Odds Ratio (tofersen/placebo)		0.75
SE of log (OR)		0.534
95% CI		(0.263, 2.126)
p-value		0.5847
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.078
95% CI		(-0.195, 0.112)
p-value		0.5952

NOTE: Only treatment emergent adverse events are summarized. A subject was counted only once under the maximum CTCAE grade (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-maxctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any serious event	13 (36.1)	36 (50.0)
RR - Relative Risk (tofersen/placebo)		1.38
SE of log (RR)		0.251
95% CI		(0.846, 2.265)
p-value		0.1949
OR - Odds Ratio (tofersen/placebo)		1.77
SE of log (OR)		0.419
95% CI		(0.778, 4.026)
p-value		0.1738
ARR - Absolute Risk Reduction (tofersen/placebo)		0.14
SE of ARR		0.099
95% CI		(-0.056, 0.334)
p-value		0.1623

Source: biib067/valueaccess/amnog4/t-sae-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	9 (25.0)	18 (25.0)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.354
95% CI		(0.500, 2.000)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.471
95% CI		(0.397, 2.519)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.088
95% CI		(-0.173, 0.173)
p-value		1.0000

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Infections and infestations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	7 (19.4)	13 (18.1)
RR - Relative Risk (tofersen/placebo)		0.93
SE of log (RR)		0.422
95% CI		(0.406, 2.123)
p-value		0.8606
OR - Odds Ratio (tofersen/placebo)		0.91
SE of log (OR)		0.521
95% CI		(0.329, 2.533)
p-value		0.8610
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.080
95% CI		(-0.171, 0.143)
p-value		0.8622

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Gastrointestinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.791
95% CI		(0.319, 7.064)
p-value		0.6080
OR - Odds Ratio (tofersen/placebo)		1.55
SE of log (OR)		0.843
95% CI		(0.296, 8.071)
p-value		0.6057
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.050
95% CI		(-0.071, 0.126)
p-value		0.5799

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Nervous system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.701
95% CI		(0.211, 3.294)
p-value		0.7949
OR - Odds Ratio (tofersen/placebo)		0.82
SE of log (OR)		0.761
95% CI		(0.185, 3.645)
p-value		0.7953
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.01
SE of ARR		0.055
95% CI		(-0.122, 0.094)
p-value		0.8005

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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General disorders and administration site conditions

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Injury, poisoning and procedural complications

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by system organ class - safety population

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Renal and urinary disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 22JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	3 (8.3)	8 (11.1)
RR - Relative Risk (tofersen/placebo)		1.33
SE of log (RR)		0.645
95% CI		(0.376, 4.725)
p-value		0.6558
OR - Odds Ratio (tofersen/placebo)		1.38
SE of log (OR)		0.710
95% CI		(0.342, 5.530)
p-value		0.6538
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.059
95% CI		(-0.088, 0.144)
p-value		0.6384

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.58
SE of log (RR)		0.518
95% CI		(0.212, 1.609)
p-value		0.2977
OR - Odds Ratio (tofersen/placebo)		0.54
SE of log (OR)		0.599
95% CI		(0.167, 1.740)
p-value		0.3010
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.071
95% CI		(-0.209, 0.070)
p-value		0.3298

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Acute respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		6.59
SE of log (RR)		1.454
95% CI		(0.381, 113.809)
p-value		0.1946
OR - Odds Ratio (tofersen/placebo)		7.14
SE of log (OR)		1.482
95% CI		(0.391, 130.282)
p-value		0.1849
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.038
95% CI		(0.000, 0.151)
p-value		0.0490

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Gastrointestinal disorders/Dysphagia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		4.56
SE of log (RR)		1.477
95% CI		(0.252, 82.478)
p-value		0.3042
OR - Odds Ratio (tofersen/placebo)		4.80
SE of log (OR)		1.505
95% CI		(0.251, 91.553)
p-value		0.2975
ARR - Absolute Risk Reduction (tofersen/placebo)		0.05
SE of ARR		0.034
95% CI		(-0.018, 0.115)
p-value		0.1563

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Pulmonary embolism

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		1.00
SE of log (RR)		0.842
95% CI		(0.192, 5.205)
p-value		1.0000
OR - Odds Ratio (tofersen/placebo)		1.00
SE of log (OR)		0.891
95% CI		(0.174, 5.735)
p-value		1.0000
ARR - Absolute Risk Reduction (tofersen/placebo)		0.00
SE of ARR		0.047
95% CI		(-0.092, 0.092)
p-value		1.0000

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one serious adverse event by preferred term - safety population

Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include preferred term with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. Preferred term is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each preferred term (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-sae-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	15 (41.7)	35 (48.6)
RR - Relative Risk (tofersen/placebo)		1.17
SE of log (RR)		0.231
95% CI		(0.741, 1.836)
p-value		0.5054
OR - Odds Ratio (tofersen/placebo)		1.32
SE of log (OR)		0.412
95% CI		(0.590, 2.971)
p-value		0.4955
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.101
95% CI		(-0.129, 0.268)
p-value		0.4922

Source: biib067/valueaccess/amnog4/t-ae-ctc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Respiratory, thoracic and mediastinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	8 (22.2)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		1.06
SE of log (RR)		0.377
95% CI		(0.507, 2.225)
p-value		0.8723
OR - Odds Ratio (tofersen/placebo)		1.08
SE of log (OR)		0.488
95% CI		(0.416, 2.813)
p-value		0.8719
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.085
95% CI		(-0.154, 0.181)
p-value		0.8709

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Infections and infestations

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	6 (16.7)	10 (13.9)
RR - Relative Risk (tofersen/placebo)		0.83
SE of log (RR)		0.474
95% CI		(0.329, 2.111)
p-value		0.7007
OR - Odds Ratio (tofersen/placebo)		0.81
SE of log (OR)		0.562
95% CI		(0.268, 2.428)
p-value		0.7020
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.03
SE of ARR		0.074
95% CI		(-0.173, 0.118)
p-value		0.7085

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Injury, poisoning and procedural complications

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	[redacted]	
RR - Relative Risk (tofersen/placebo)		6.59
SE of log (RR)		1.454
95% CI		(0.381, 113.809)
p-value		0.1946
OR - Odds Ratio (tofersen/placebo)		7.14
SE of log (OR)		1.482
95% CI		(0.391, 130.282)
p-value		0.1849
ARR - Absolute Risk Reduction (tofersen/placebo)		0.08
SE of ARR		0.038
95% CI		(0.000, 0.151)
p-value		0.0490

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Gastrointestinal disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.811
95% CI		(0.255, 6.131)
p-value		0.7833
OR - Odds Ratio (tofersen/placebo)		1.27
SE of log (OR)		0.863
95% CI		(0.234, 6.882)
p-value		0.7827
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.049
95% CI		(-0.081, 0.109)
p-value		0.7747

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Nervous system disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	5 (6.9)
RR - Relative Risk (tofersen/placebo)		1.25
SE of log (RR)		0.811
95% CI		(0.255, 6.131)
p-value		0.7833
OR - Odds Ratio (tofersen/placebo)		1.27
SE of log (OR)		0.863
95% CI		(0.234, 6.882)
p-value		0.7827
ARR - Absolute Risk Reduction (tofersen/placebo)		0.01
SE of ARR		0.049
95% CI		(-0.081, 0.109)
p-value		0.7747

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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General disorders and administration site conditions

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	1 (2.8)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		2.00
SE of log (RR)		1.099
95% CI		(0.232, 17.247)
p-value		0.5283
OR - Odds Ratio (tofersen/placebo)		2.06
SE of log (OR)		1.137
95% CI		(0.222, 19.126)
p-value		0.5254
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.038
95% CI		(-0.048, 0.103)
p-value		0.4701

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by system organ class - safety population

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Renal and urinary disorders

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-soc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 19JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	6 (16.7)	7 (9.7)
RR - Relative Risk (tofersen/placebo)		0.58
SE of log (RR)		0.518
95% CI		(0.212, 1.609)
p-value		0.2977
OR - Odds Ratio (tofersen/placebo)		0.54
SE of log (OR)		0.599
95% CI		(0.167, 1.740)
p-value		0.3010
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.07
SE of ARR		0.071
95% CI		(-0.209, 0.070)
p-value		0.3298

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Infections and infestations/Pneumonia aspiration

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	2 (5.6)	6 (8.3)
RR - Relative Risk (tofersen/placebo)		1.50
SE of log (RR)		0.791
95% CI		(0.319, 7.064)
p-value		0.6080
OR - Odds Ratio (tofersen/placebo)		1.55
SE of log (OR)		0.843
95% CI		(0.296, 8.071)
p-value		0.6057
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.050
95% CI		(-0.071, 0.126)
p-value		0.5799

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Acute respiratory failure

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	[redacted]	
RR - Relative Risk (tofersen/placebo)		5.58
SE of log (RR)		1.463
95% CI		(0.317, 98.127)
p-value		0.2403
OR - Odds Ratio (tofersen/placebo)		5.95
SE of log (OR)		1.491
95% CI		(0.320, 110.610)
p-value		0.2318
ARR - Absolute Risk Reduction (tofersen/placebo)		0.06
SE of ARR		0.036
95% CI		(-0.009, 0.133)
p-value		0.0881

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Pulmonary embolism

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	1 (2.8)	4 (5.6)
RR - Relative Risk (tofersen/placebo)		2.00
SE of log (RR)		1.099
95% CI		(0.232, 17.247)
p-value		0.5283
OR - Odds Ratio (tofersen/placebo)		2.06
SE of log (OR)		1.137
95% CI		(0.222, 19.126)
p-value		0.5254
ARR - Absolute Risk Reduction (tofersen/placebo)		0.03
SE of ARR		0.038
95% CI		(-0.048, 0.103)
p-value		0.4701

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Respiratory, thoracic and mediastinal disorders/Dyspnoea

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	3 (8.3)	2 (2.8)
RR - Relative Risk (tofersen/placebo)		0.33
SE of log (RR)		0.890
95% CI		(0.058, 1.907)
p-value		0.2169
OR - Odds Ratio (tofersen/placebo)		0.31
SE of log (OR)		0.937
95% CI		(0.050, 1.972)
p-value		0.2167
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.050
95% CI		(-0.153, 0.042)
p-value		0.2662

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

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Infections and infestations/Pneumonia

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	2 (5.6)	1 (1.4)
RR - Relative Risk (tofersen/placebo)		0.25
SE of log (RR)		1.208
95% CI		(0.023, 2.666)
p-value		0.2510
OR - Odds Ratio (tofersen/placebo)		0.24
SE of log (OR)		1.242
95% CI		(0.021, 2.733)
p-value		0.2499
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.04
SE of ARR		0.041
95% CI		(-0.121, 0.038)
p-value		0.3047

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event with CTCAE grade >= 3 by preferred term - safety population

Gastrointestinal disorders/Constipation

	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with any grade >= 3 event	[redacted]	
RR - Relative Risk (tofersen/placebo)		0.10
SE of log (RR)		1.536
95% CI		(0.005, 2.058)
p-value		0.1362
OR - Odds Ratio (tofersen/placebo)		0.10
SE of log (OR)		1.563
95% CI		(0.004, 2.037)
p-value		0.1324
ARR - Absolute Risk Reduction (tofersen/placebo)		-0.06
SE of ARR		0.042
95% CI		(-0.144, 0.022)
p-value		0.1519

NOTE 1: Include system organ class with >=5% patients with events OR (at least 10 patients with events and >= 1% patients with events) in at least one treatment group. System organ class is presented in decreasing frequency of event occurrence in the toferson 100mg group.
NOTE 2: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class (MedDRA version 24.0).
Source: biib067/valueaccess/amnog4/t-ae-ctc-pt-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 18JUL2023

233AS101 and 233AS102 ISS: Number of subjects with at least one adverse event leading to drug discontinuation - safety population

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	CL ITT: 233AS101 Part C and 233AS102 (Part C subjects)	
	placebo + delayed-start tofersen 100 mg (N=36)	**Early-start tofersen 100 mg (N=72)**
Number of subjects with at least one adverse event leading to drug discontinuation	6 (16.7)	17 (23.6)
RR - Relative Risk (tofersen/placebo)		1.42
SE of log (RR)		0.429
95% CI		(0.611, 3.283)
p-value		0.4166
OR - Odds Ratio (tofersen/placebo)		1.55
SE of log (OR)		0.526
95% CI		(0.551, 4.336)
p-value		0.4082
ARR - Absolute Risk Reduction (tofersen/placebo)		0.07
SE of ARR		0.080
95% CI		(-0.087, 0.226)
p-value		0.3840

Source: biib067/valueaccess/amnog4/t-ae-disc-event-cl.sas **Data Cutoff:** 28FEB2023 **Run Date:** 15JUL2023

233AS101 and 233AS102 ISS: Adverse events that led to discontinuation of study drug by system organ class and preferred term - safety population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72) n (%)	placebo (N=36) n (%)	tofersen 100 mg (N=104) n (%)	Total tofersen 100 mg (N=147) n (%)	Total tofersen all doses (N=166) n (%)
Number of subjects with any event that led to discontinuation	4 (5.6)	0	23 (22.1)	30 (20.4)	31 (18.7)
Respiratory, thoracic and mediastinal disorders	[redacted]		12 (11.5)	16 (10.9)	16 (9.6)
Respiratory failure	0	0	9 (8.7)	11 (7.5)	11 (6.6)
Respiratory arrest	0	0	2 (1.9)	2 (1.4)	2 (1.2)
Dyspnoea	0	0	0	1 (0.7)	1 (0.6)
Pneumonitis aspiration	0	0	0	1 (0.7)	1 (0.6)
Pulmonary embolism	[redacted]		1 (1.0)	1 (0.7)	1 (0.6)
Nervous system disorders	0	0	2 (1.9)	5 (3.4)	5 (3.0)
Amyotrophic lateral sclerosis	0	0	2 (1.9)	3 (2.0)	3 (1.8)
Neurosarcoidosis	0	0	0	1 (0.7)	1 (0.6)
Vocal cord paralysis	0	0	0	1 (0.7)	1 (0.6)
Infections and infestations	[redacted]		3 (2.9)	3 (2.0)	4 (2.4)
Pneumonia aspiration	0	0	1 (1.0)	1 (0.7)	2 (1.2)
Myelitis	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Pulmonary sepsis	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Septic shock	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardiac disorders	[redacted]		3 (2.9)	3 (2.0)	3 (1.8)
Cardiac arrest	0	0	1 (1.0)	1 (0.7)	1 (0.6)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 25.1).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla4/t-ae-socpt.sas:t-ae-socpt-disc.rtf **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISS: Adverse events that led to discontinuation of study drug by system organ class and preferred term - safety population

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	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72) n (%)	placebo (N=36) n (%)	tofersen 100 mg (N=104) n (%)	Total tofersen 100 mg (N=147) n (%)	Total tofersen all doses (N=166) n (%)
Cardiac failure congestive	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardio-respiratory arrest	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Gastrointestinal disorders	0	0	1 (1.0)	2 (1.4)	2 (1.2)
Gastritis	0	0	0	1 (0.7)	1 (0.6)
Pancreatitis	0	0	0	1 (0.7)	1 (0.6)
Salivary hypersecretion	0	0	1 (1.0)	1 (0.7)	1 (0.6)
General disorders and administration site conditions	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Sudden death	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Injury, poisoning and procedural complications	[redacted]		1 (1.0)	1 (0.7)	1 (0.6)
Meningitis chemical	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Investigations	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Blood alkaline phosphatase increased	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Musculoskeletal and connective tissue disorders	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Muscular weakness	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Surgical and medical procedures	0	0	0	1 (0.7)	1 (0.6)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 25.1).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla4/t-ae-socpt.sas:t-ae-socpt-disc.rtf **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISS: Adverse events that led to discontinuation of study drug by system organ class and preferred term - safety population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72) n (%)	placebo (N=36) n (%)	tofersen 100 mg (N=104) n (%)	Total tofersen 100 mg (N=147) n (%)	Total tofersen all doses (N=166) n (%)
Euthanasia	0	0	0	1 (0.7)	1 (0.6)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 25.1).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla4/t-ae-socpt.sas:t-ae-socpt-disc.rtf **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISS: Adverse events that led to withdrawal from study by system organ class and preferred term - safety population

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	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72) n (%)	placebo (N=36) n (%)	tofersen 100 mg (N=104) n (%)	Total tofersen 100 mg (N=147) n (%)	Total tofersen all doses (N=166) n (%)
Number of subjects with any event that led to withdrawal	[redacted]		22 (21.2)	28 (19.0)	31 (18.7)
Respiratory, thoracic and mediastinal disorders	0	0	12 (11.5)	16 (10.9)	17 (10.2)
Respiratory failure	0	0	10 (9.6)	12 (8.2)	13 (7.8)
Respiratory arrest	0	0	2 (1.9)	2 (1.4)	2 (1.2)
Dyspnoea	0	0	0	1 (0.7)	1 (0.6)
Pneumonitis aspiration	0	0	0	1 (0.7)	1 (0.6)
Infections and infestations	[redacted]		4 (3.8)	4 (2.7)	5 (3.0)
Myelitis	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Pneumonia	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Pneumonia aspiration	0	0	0	0	1 (0.6)
Pulmonary sepsis	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Septic shock	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardiac disorders	[redacted]		3 (2.9)	3 (2.0)	4 (2.4)
Cardiac arrest	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardiac failure congestive	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardio-respiratory arrest	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Cardiovascular disorder	0	0	0	0	1 (0.6)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 25.1).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

Source: biib067/iss/iss-bla4/t-ae-socpt.sas:t-ae-socpt-wd.rtf **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

233AS101 and 233AS102 ISS: Adverse events that led to withdrawal from study by system organ class and preferred term - safety population

	RC: 233AS101 Part C (Part C subjects) placebo-controlled period		CL: 233AS101 Part C and 233AS102 (Part C subjects) tofersen treated period	ABCL: Overall 233AS101 and 233AS102 (Parts A, B and C subjects) tofersen treated period	
	tofersen 100 mg (N=72) n (%)	placebo (N=36) n (%)	tofersen 100 mg (N=104) n (%)	Total tofersen 100 mg (N=147) n (%)	Total tofersen all doses (N=166) n (%)
General disorders and administration site conditions	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Sudden death	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Injury, poisoning and procedural complications	[redacted]		1 (1.0)	1 (0.7)	1 (0.6)
Meningitis chemical	1 (1.4)	0	1 (1.0)	1 (0.7)	1 (0.6)
Musculoskeletal and connective tissue disorders	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Muscular weakness	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Nervous system disorders	0	0	0	1 (0.7)	1 (0.6)
Amyotrophic lateral sclerosis	0	0	0	1 (0.7)	1 (0.6)
Surgical and medical procedures	0	0	0	1 (0.7)	1 (0.6)
Euthanasia	0	0	0	1 (0.7)	1 (0.6)

NOTE 1: Only treatment emergent adverse events are summarized. A subject was counted only once within each system organ class and preferred term (MedDRA version 25.1).

NOTE 2: System organ class and preferred term are presented in decreasing frequency of the table's rightmost column.

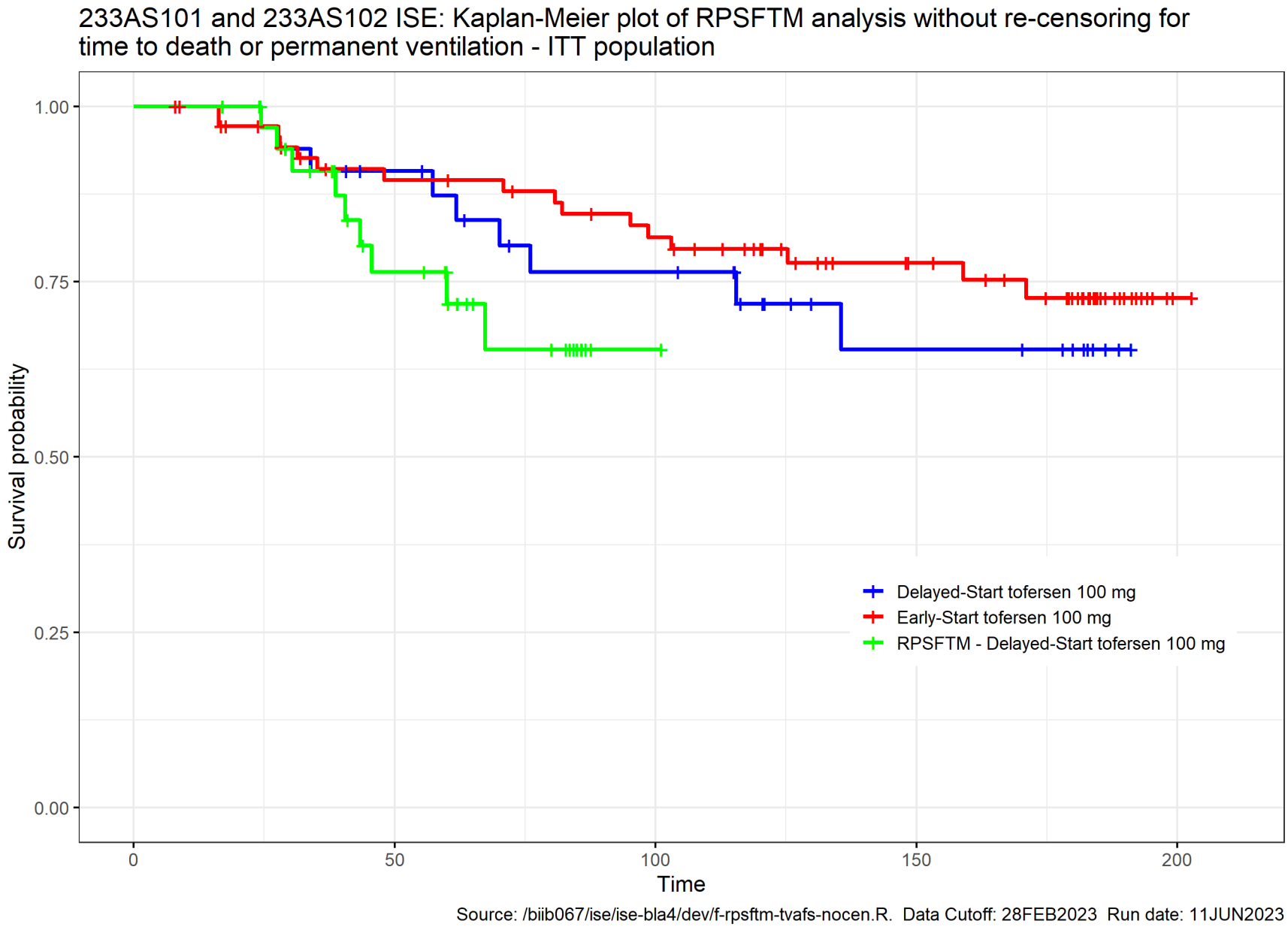
Source: biib067/iss/iss-bla4/t-ae-socpt.sas:t-ae-socpt-wd.rtf **Data Cutoff:** 28FEB2023 **Run Date:** 22MAY2023

Table of Contents

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis without re-censoring for time to death or permanent ventilation – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM without re-censoring	0.22 (0.082, 0.610)	0.0035	0.0027

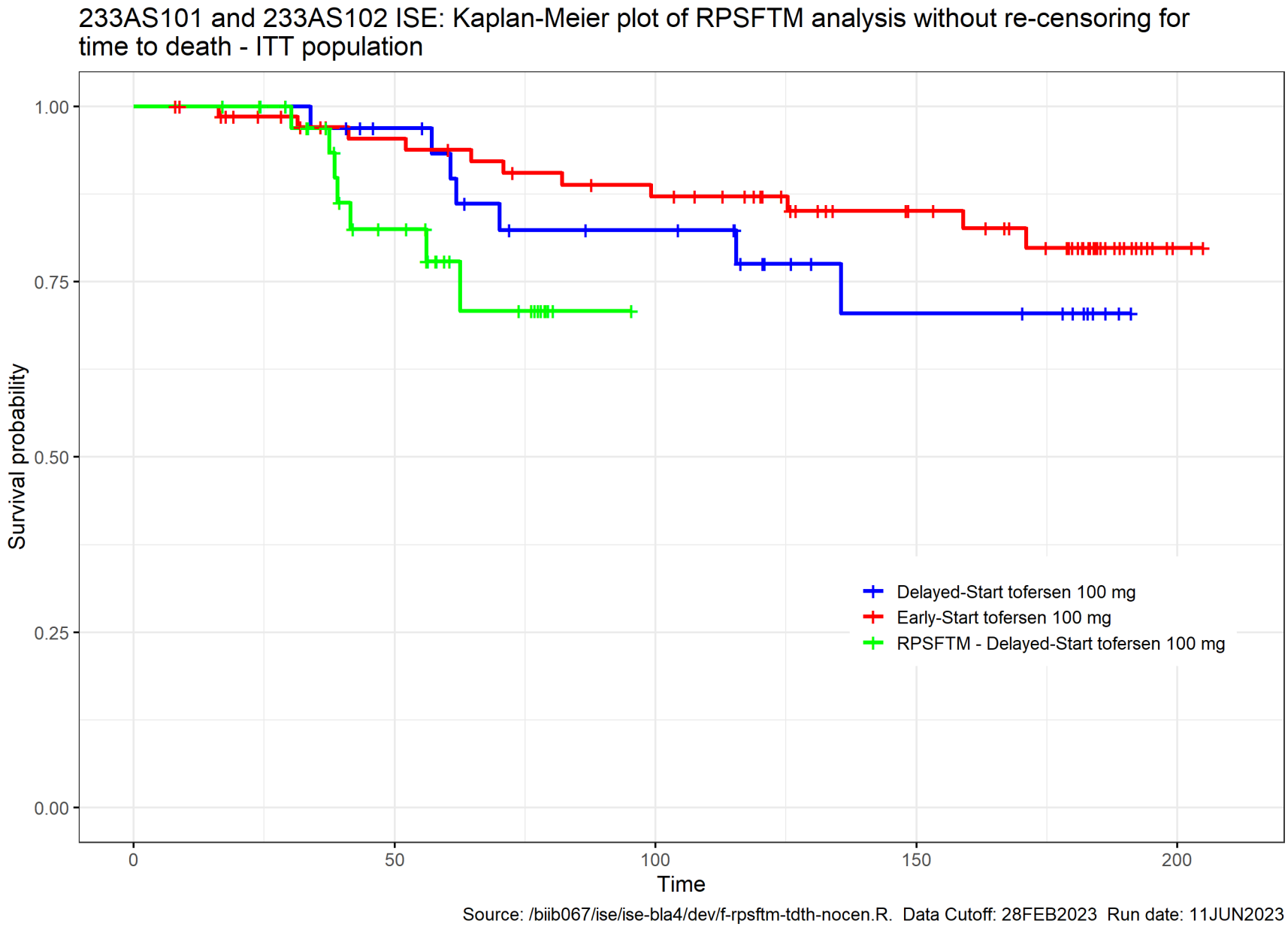
Source: /biib067/ise/ise-bla4/dev/t-rpsftm-tvafs-nocen.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis without re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
RPSFTM - Delayed-Start tofersen 100 mg
Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tvafs-nocen.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis without re-censoring for time to death - ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM without re-censoring	0.12 (0.033, 0.433)	0.0012	0.0012

Source: /biib067/ise/ise-bla4/dev/t-rpsftm-tdth-nocen.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023

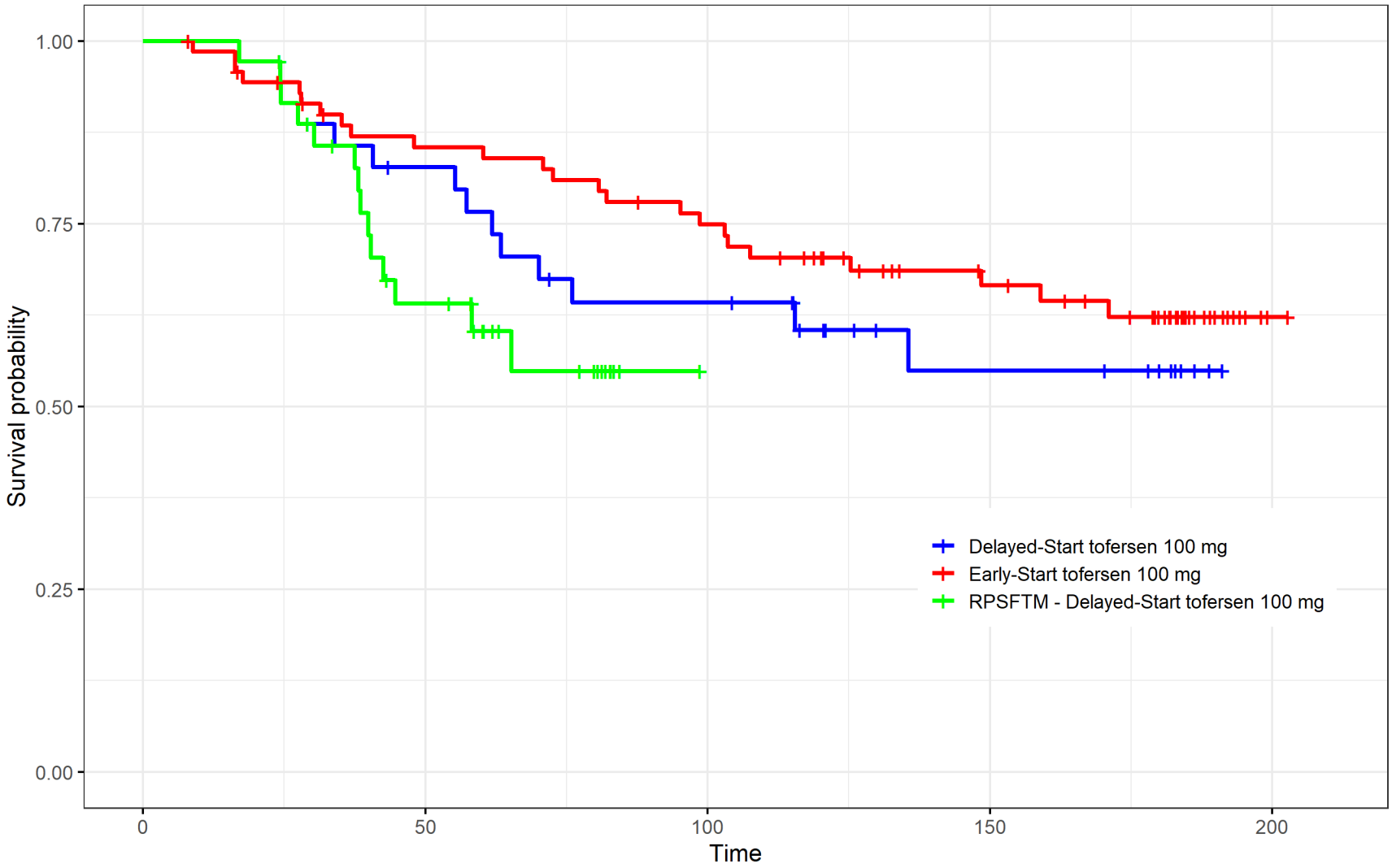

233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis without re-censoring for time to death - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
RPSFTM - Delayed-Start tofersen 100 mg
Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tdth-nocen.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis without re-censoring for time to death, permanent ventilation or withdrawal due to disease progression – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM without re-censoring	0.25 (0.112, 0.560)	8e-04	5e-04

Source: /biib067/fda/ise/ise-bla4/t-rpsftm-tvafsdp-nocen.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis without re-censoring for time to death, permanent ventilation, or withdrawal due to disease progression - ITT population

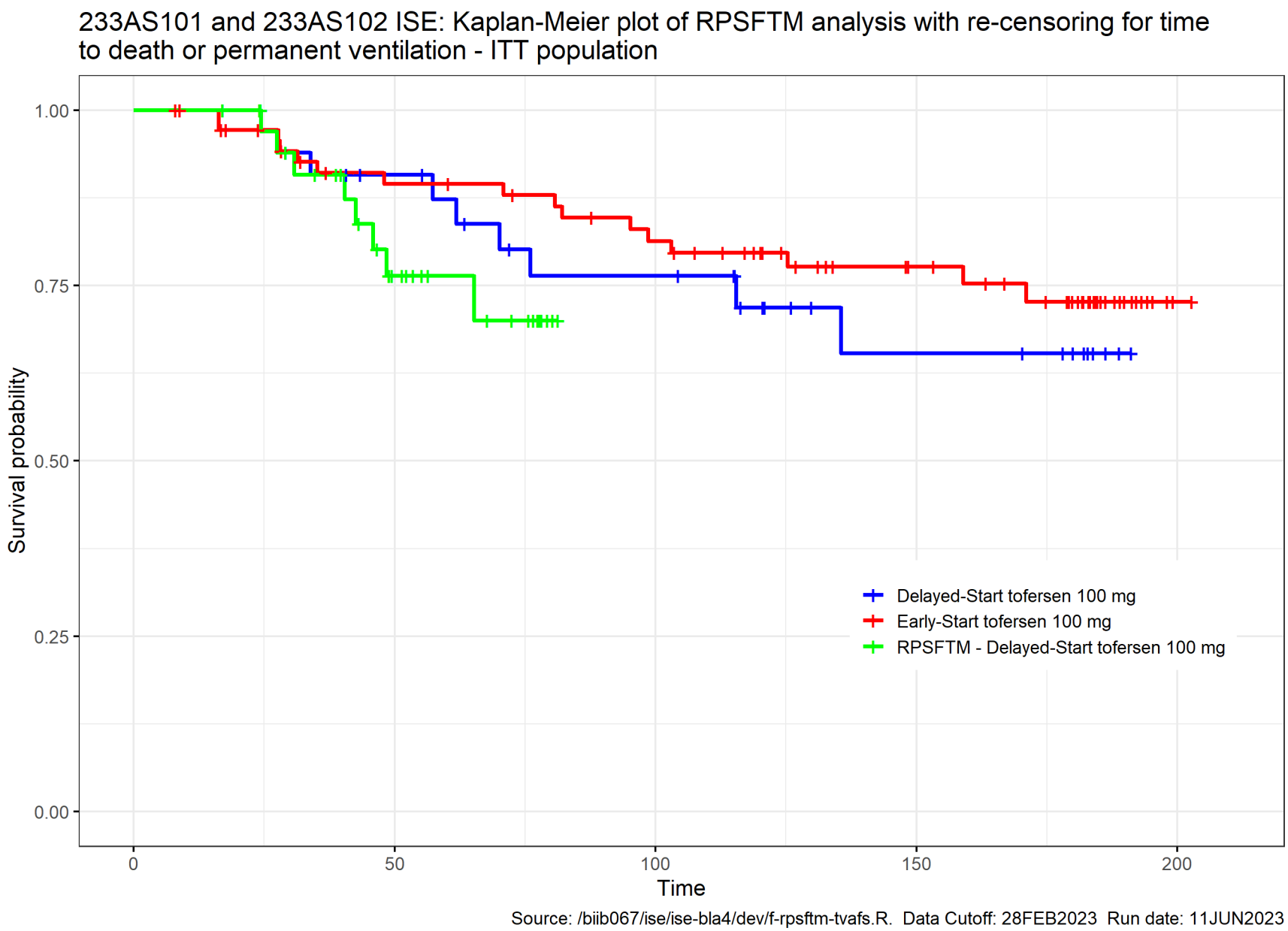


Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tvafsdp-nocen.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis with re-censoring for time to death or permanent ventilation – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM with re-censoring	0.24 (0.083, 0.698)	0.0087	0.0110

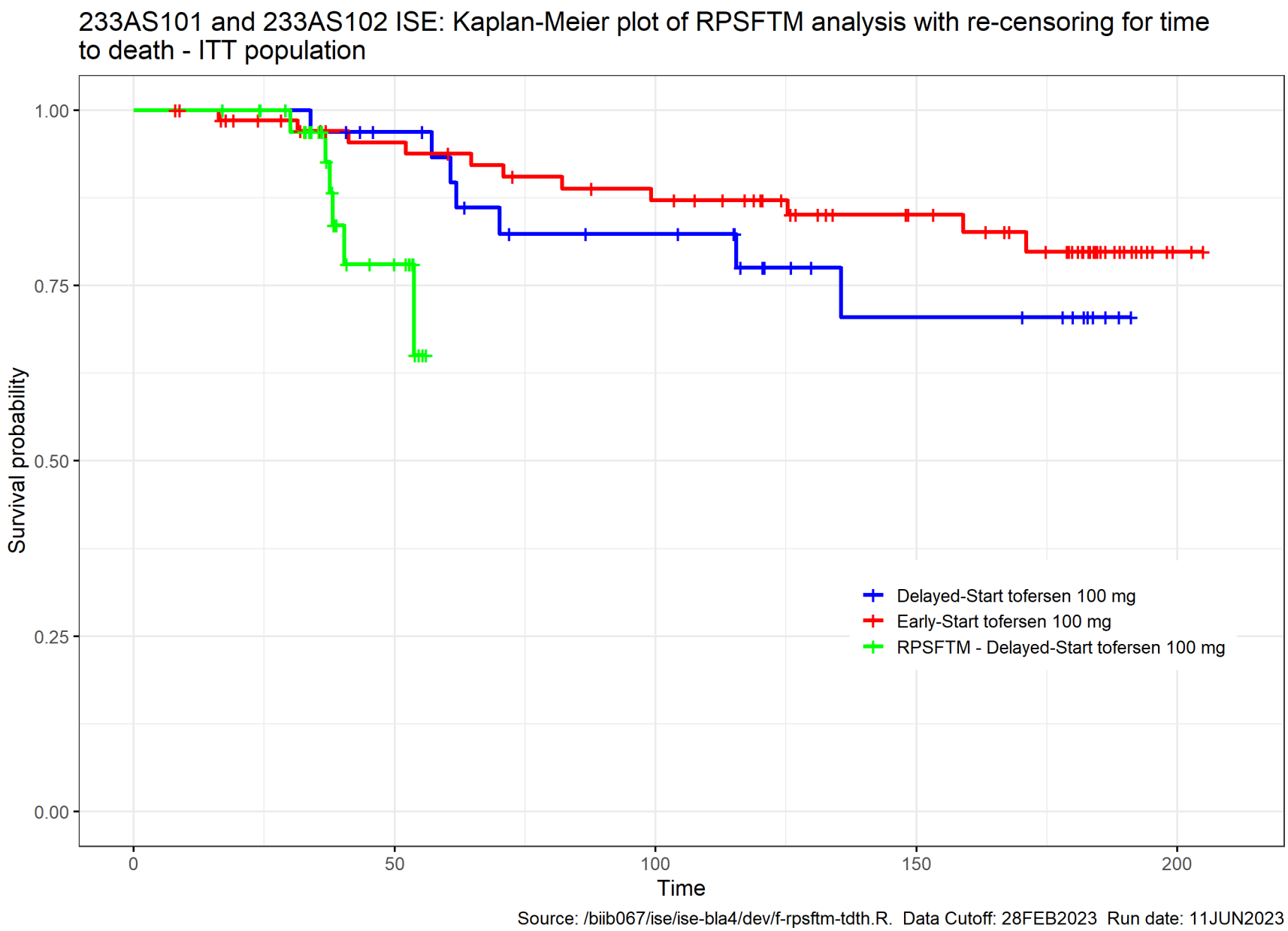
Source: /biib067/ise/ise-bla4/dev/t-rpsftm-tvafs.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis with re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
RPSFTM - Delayed-Start tofersen 100 mg
Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tvafs.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis with re-censoring for time to death – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM with re-censoring	0.08 (0.018, 0.373)	0.0012	9e-04

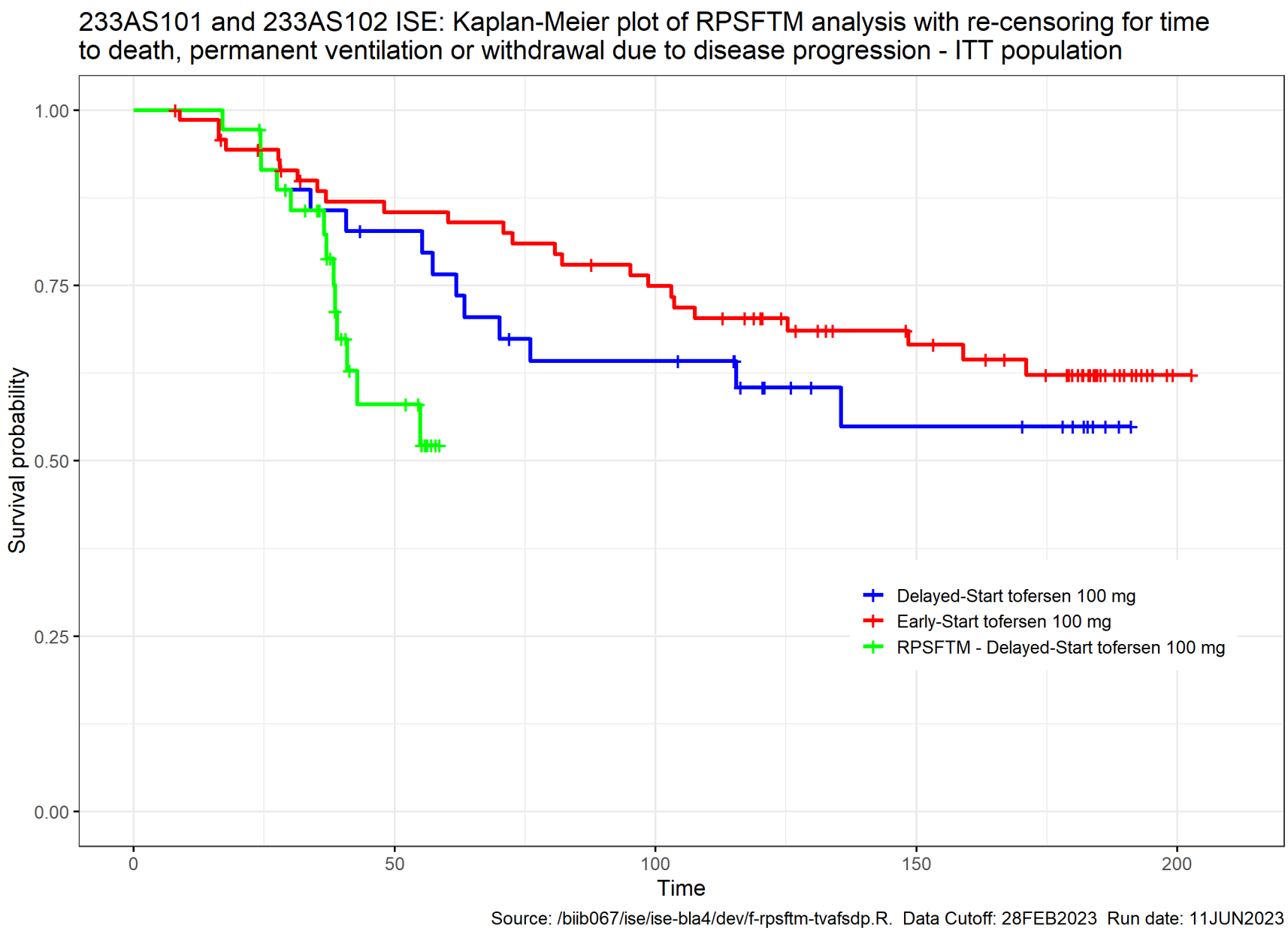
Source: /biib067/ise/ise-bla4/dev/t-rpsftm-tdth.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis with re-censoring for time to death - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
RPSFTM - Delayed-Start tofersen 100 mg
Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tdth.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis with re-censoring for time to death, permanent ventilation or withdrawal due to disease progression – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM with re-censoring	0.21 (0.086, 0.511)	6e-04	3e-04

Source: /biib067/ise/ise-bla4/dev/t-rpsftm-tvafsdp.R. Data Cutoff: 28FEB2023 Run date: 02JUN2023

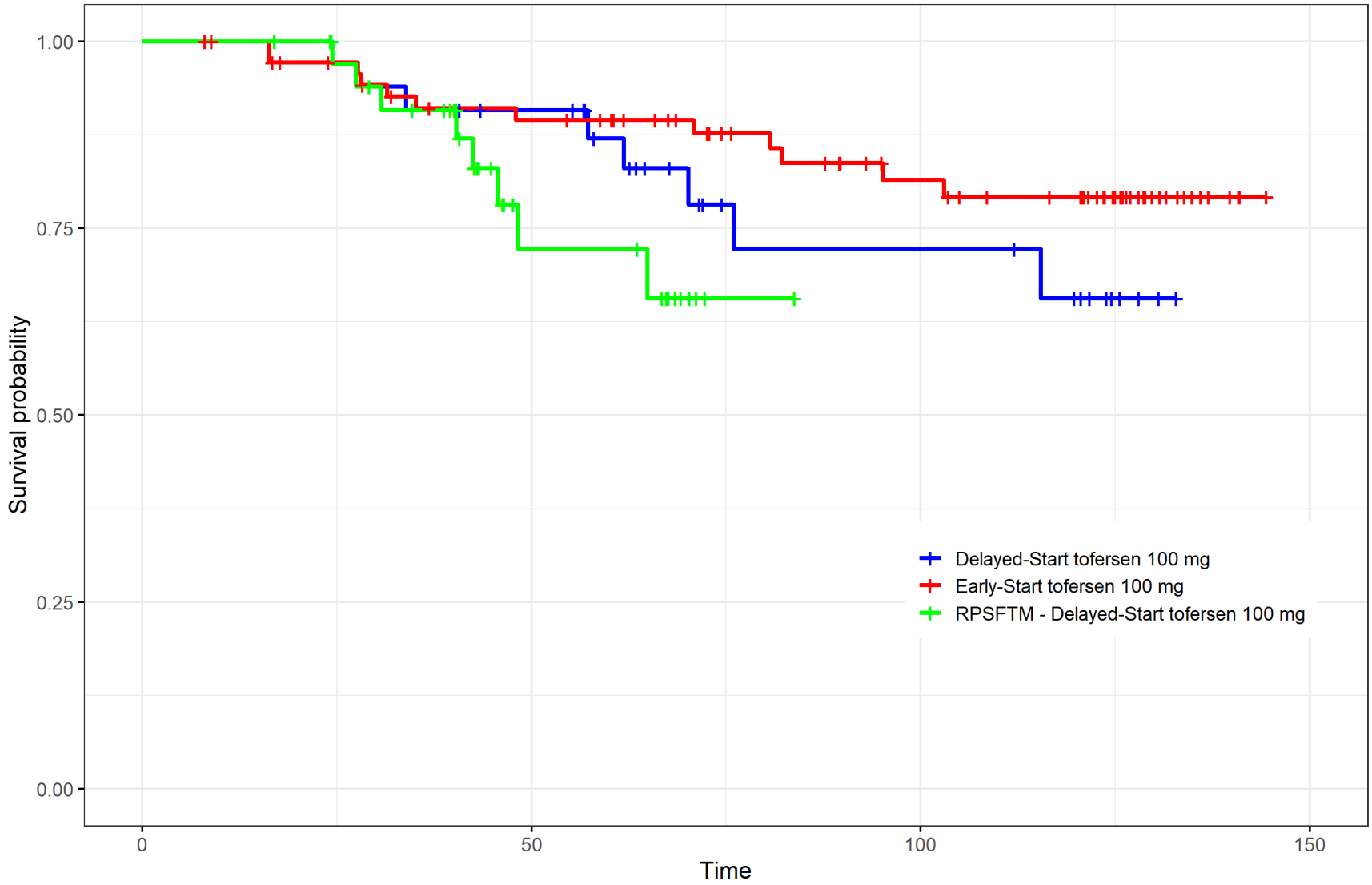

233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis with re-censoring for time to death, permanent ventilation or withdrawal due to disease progression - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
RPSFTM - Delayed-Start tofersen 100 mg
Source: /biib067/ise/ise-bla4/dev/f-rpsftm-tvafsdp.R. Data Cutoff: 28FEB2023 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis without re-censoring for time to death or permanent ventilation – ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM without re-censoring	0.20 (0.064, 0.590)	0.0038	0.0045

Source: /biib067/ema/ise-bla2-d120/dev/t-rpsftm-tvafs-nocen.R. Data Cutoff: 16JAN2022 Run date: 02JUN2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis without re-censoring for time to death or permanent ventilation - ITT population



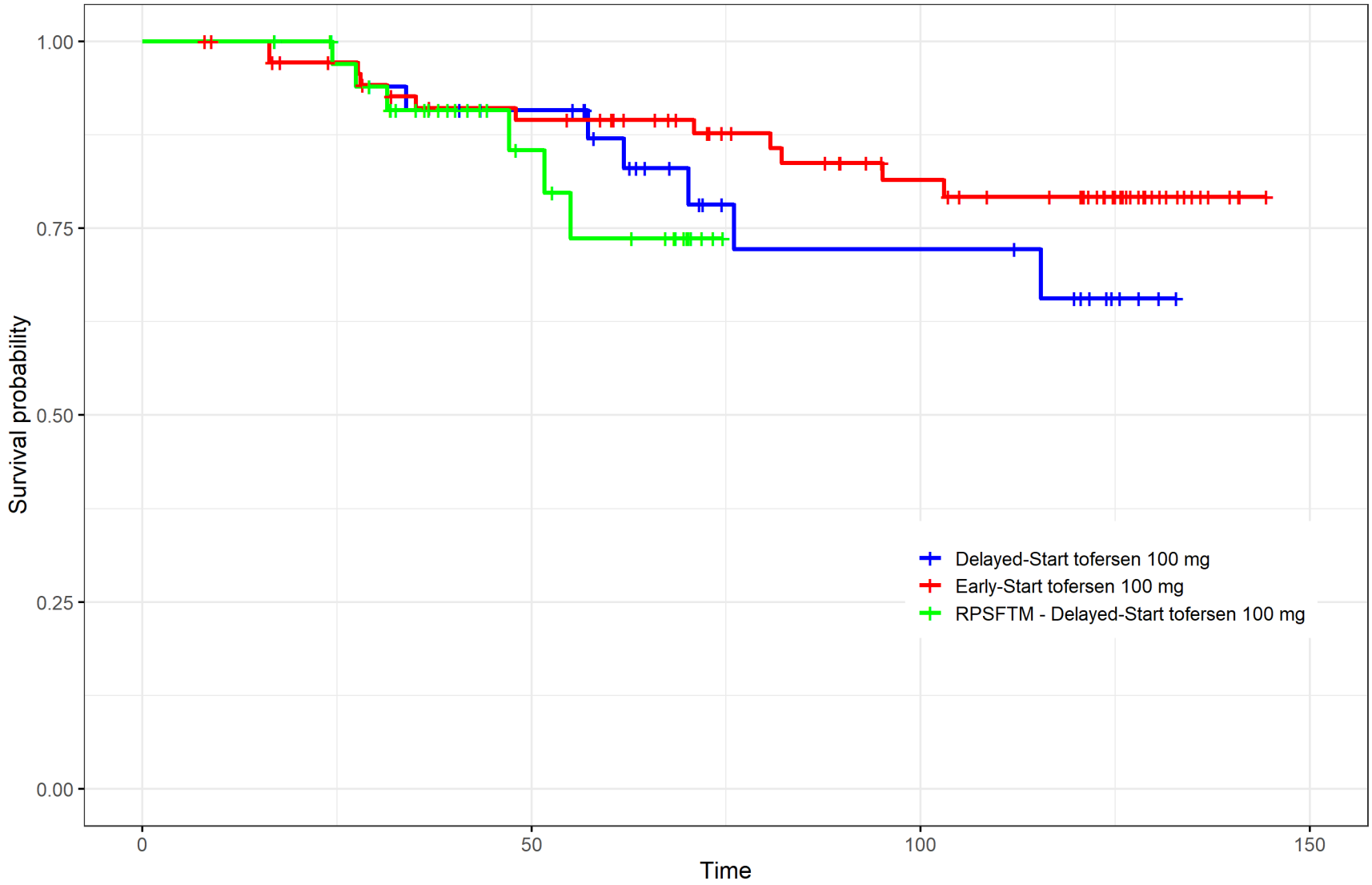
Source: /biib067/ema/ise-bla2-d120/dev/f-rpsftm-tvafs-nocen.R. Data Cutoff: 16JAN2022 Run date: 11JUN2023

233AS101 and 233AS102 ISE: Summary of RPSFTM analysis with re-censoring for time to death or permanent ventilation - ITT population

Analysis	HR from Cox	Cox p-value	Log-rank test p-value
RPSFTM with re-censoring	0.28 (0.087, 0.917)	0.0354	0.0608

Source: /biib067/ema/ise-bla2-d120/dev/t-rpsftm-tvafs.R. Data Cutoff: 16JAN2022 Run date: 02JUN2023

233AS101 and 233AS102 ISE: Kaplan-Meier plot of RPSFTM analysis with re-censoring for time to death or permanent ventilation - ITT population



Source: /biib067/ema/ise-bla2-d120/dev/f-rpsftm-tvafs.R. Data Cutoff: 16JAN2022 Run date: 11JUN2023

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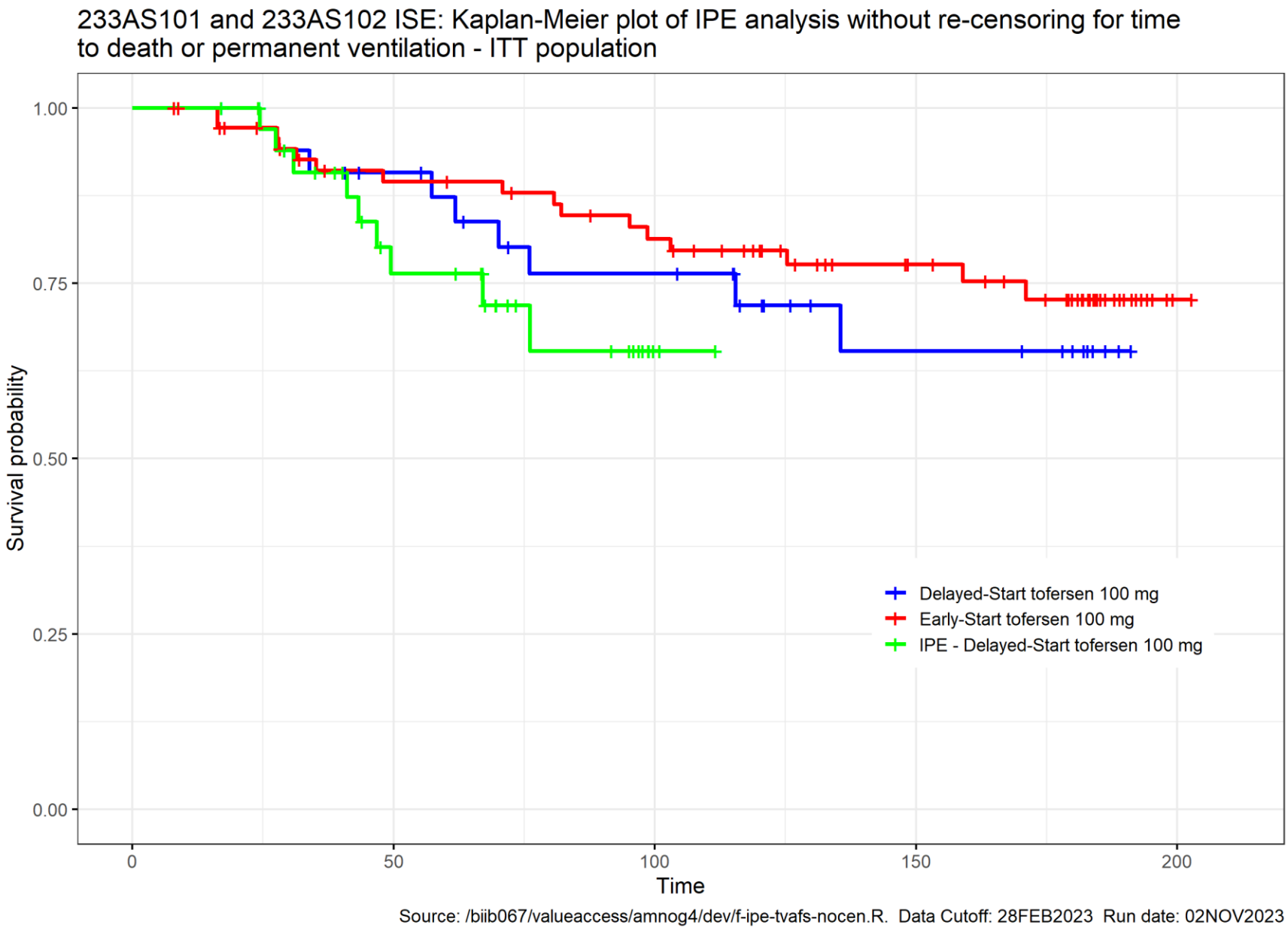
233AS101 and 233AS102 ISE: Summary of IPE analysis without re-censoring for time to death or permanent ventilation - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE without re-censoring	0.25 (0.096, 0.668)	(0.053, 1.217)	0.0055	0.0054

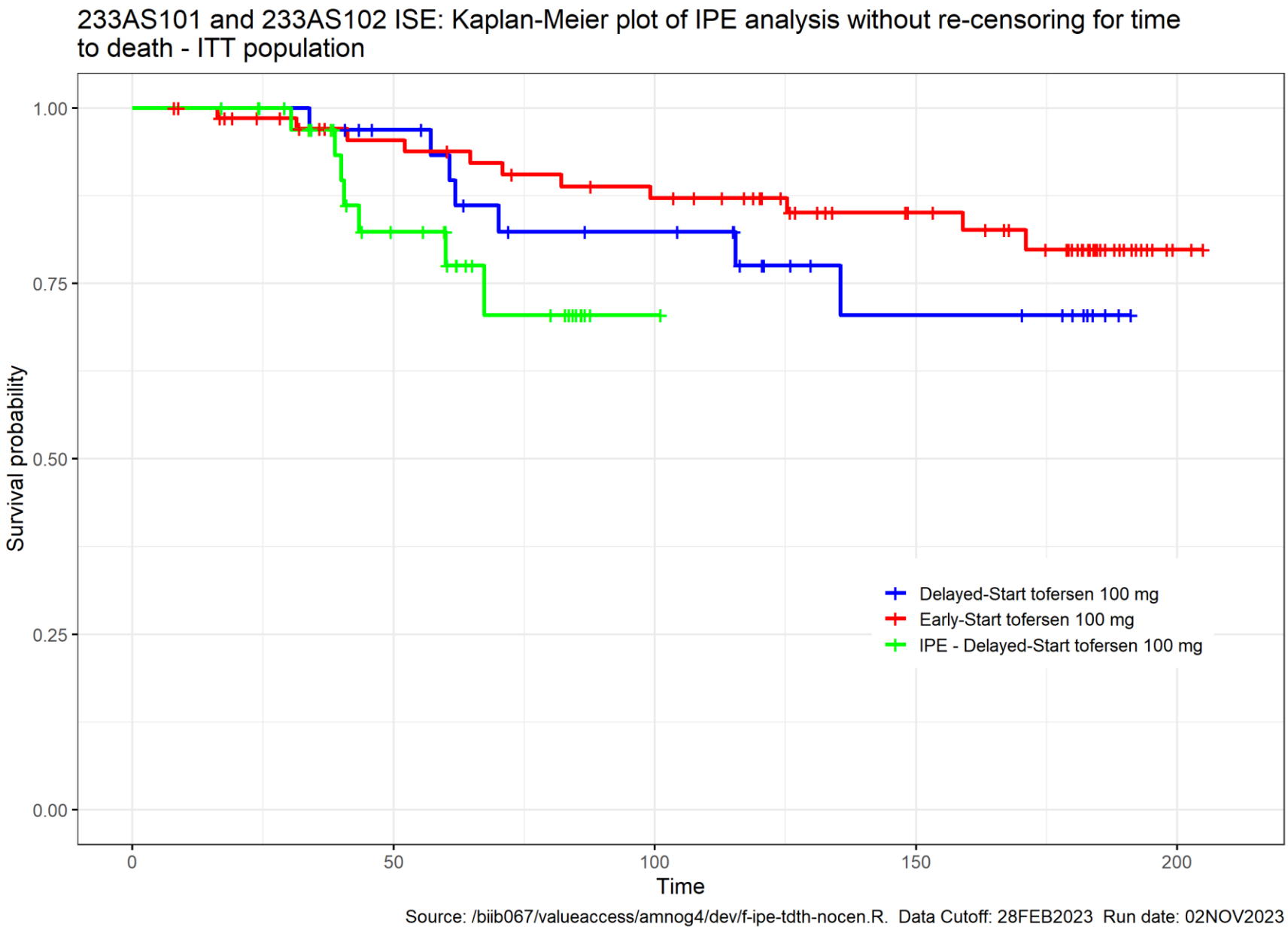
* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog4/dev/t-ipe-tvafs-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis without re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tvafs-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis without re-censoring for time to death - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE without re-censoring	0.13 (0.039, 0.468)	(0.018, 1.034)	0.0016	0.0016

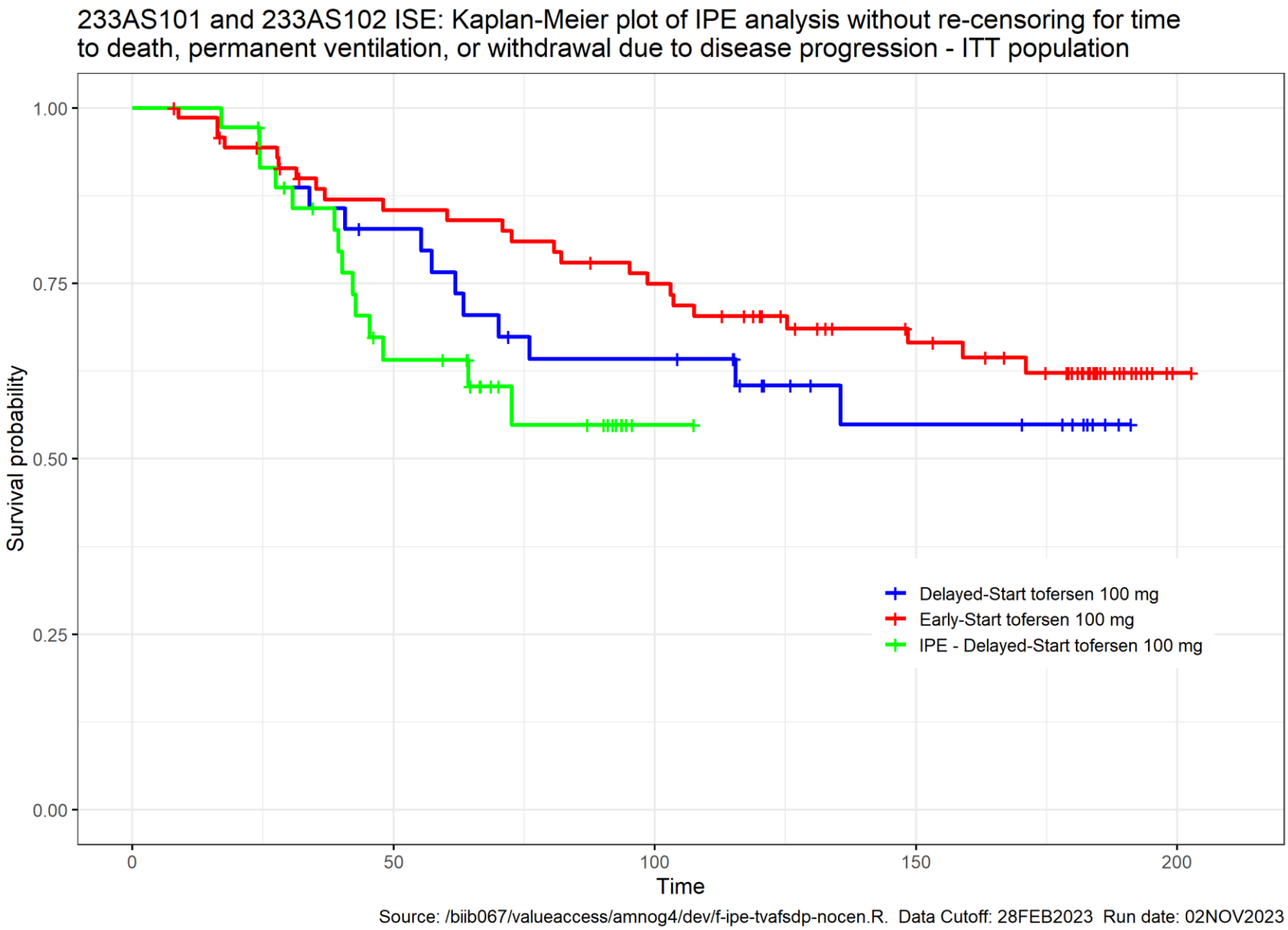
* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog4/dev/t-ipe-tdth-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis without re-censoring for time to death - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tdth-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis without re-censoring for time to death, permanent ventilation or withdrawal due to disease progression - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE without re-censoring	0.27 (0.123, 0.597)	(0.074, 0.992)	0.0012	8e-04

* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog4/t-ipe-tvafsdp-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis without re-censoring for time to death, permanent ventilation, or withdrawal due to disease progression - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tvafsdp-nocen.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis with re-censoring for time to death or permanent ventilation - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE with re-censoring	0.25 (0.089, 0.719)	(0.053, 1.218)	0.0099	0.0110

* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
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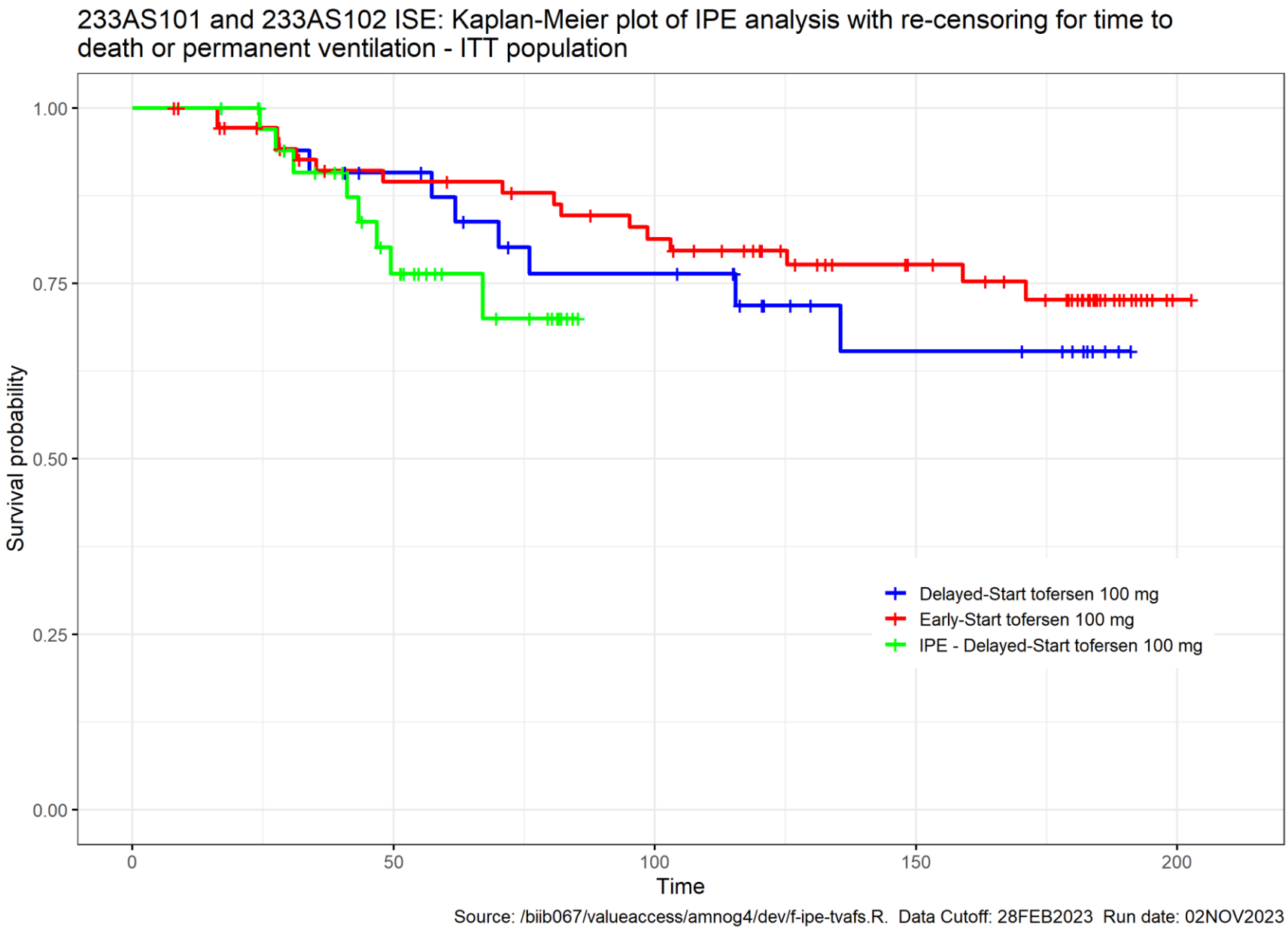
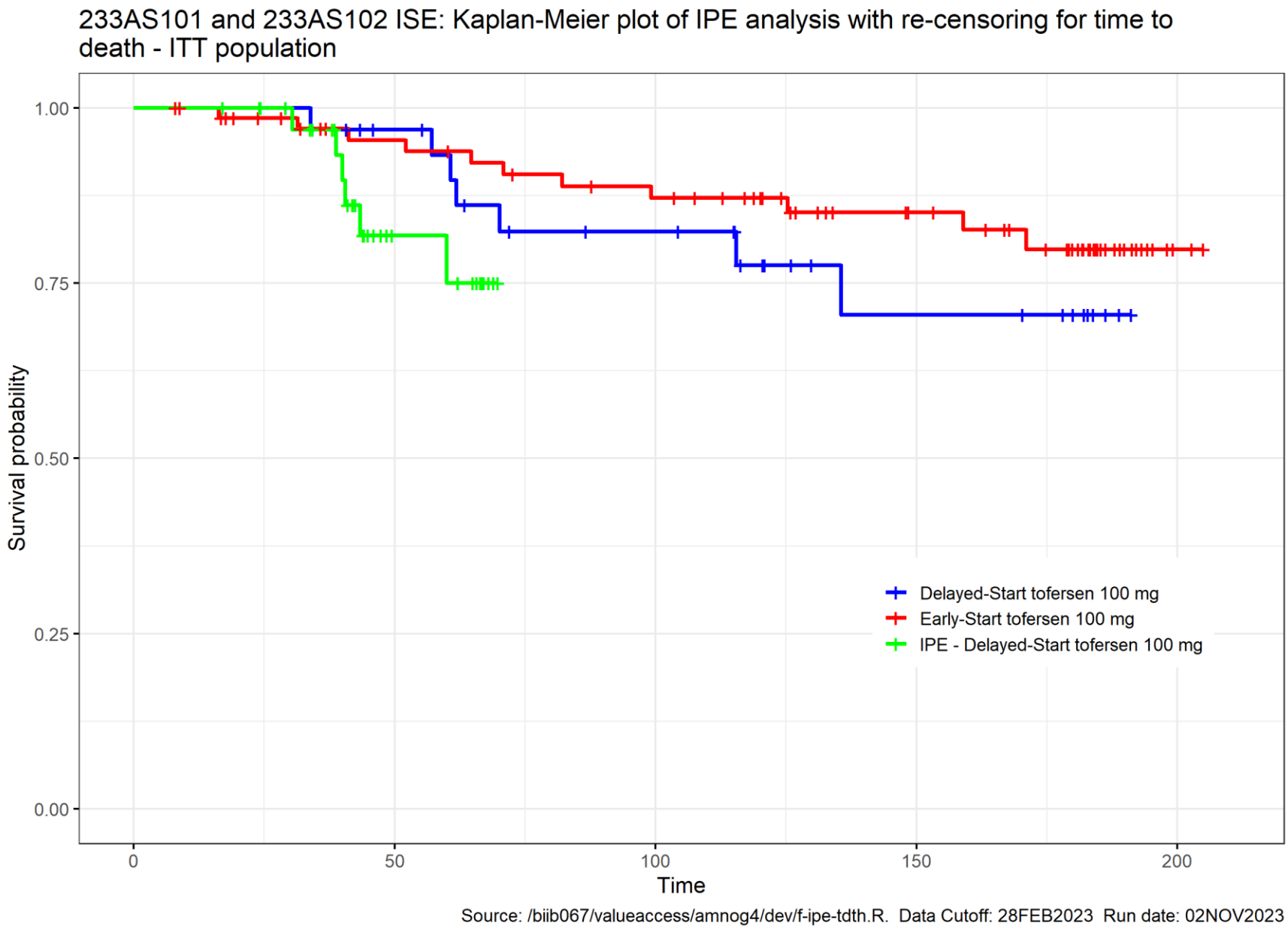
Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis with re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tvafs.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis with re-censoring for time to death - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE with re-censoring	0.11 (0.028, 0.468)	(0.013, 1.036)	0.0026	0.0024

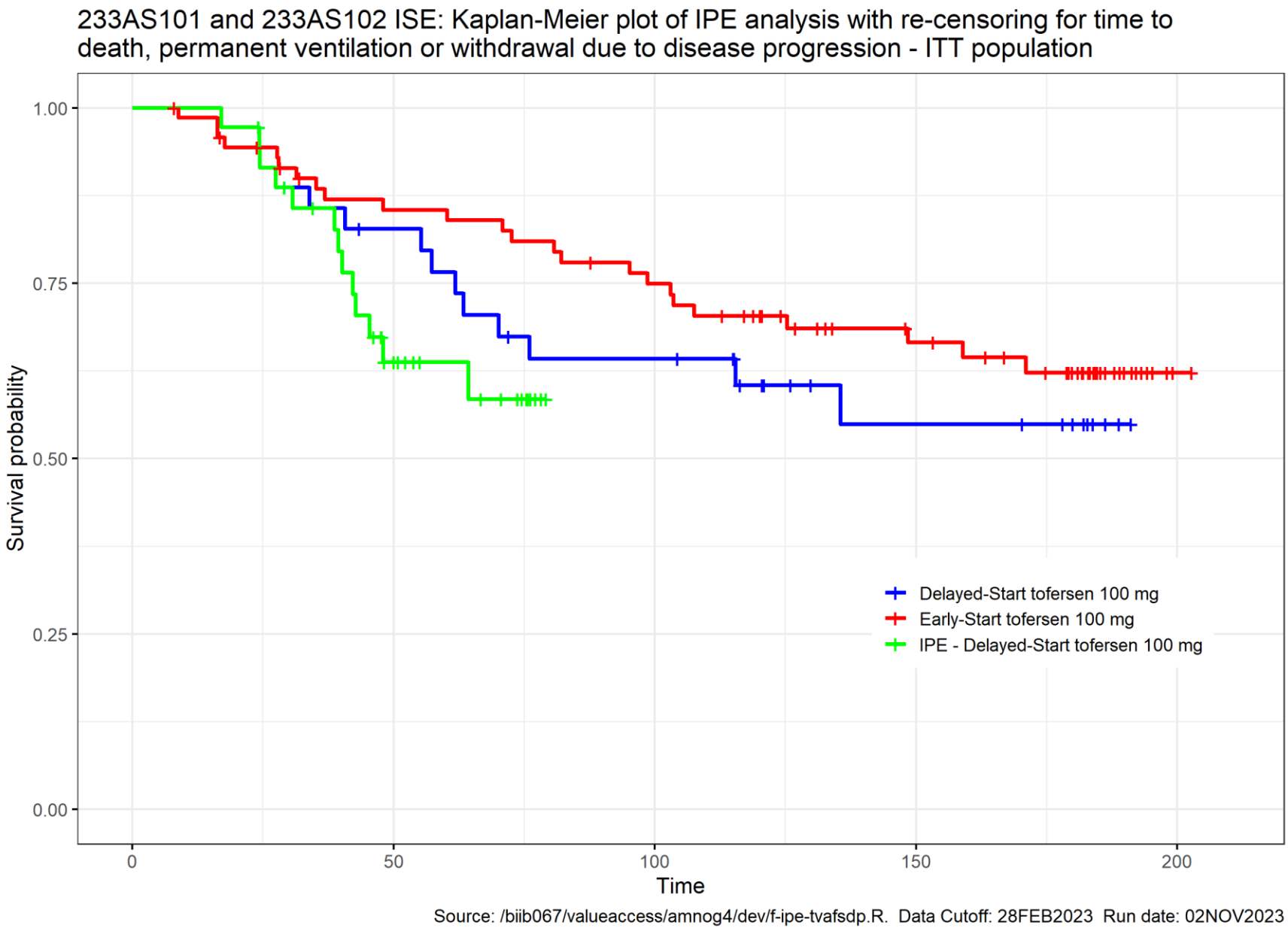
* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog4/dev/t-ipe-tdth.R. Data Cutoff: 28FEB2023
Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis with re-censoring for time to death - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tdth.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis with re-censoring for time to death, permanent ventilation or withdrawal due to disease progression - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE with re-censoring	0.26 (0.114, 0.610)	(0.070, 0.992)	0.0018	0.0011

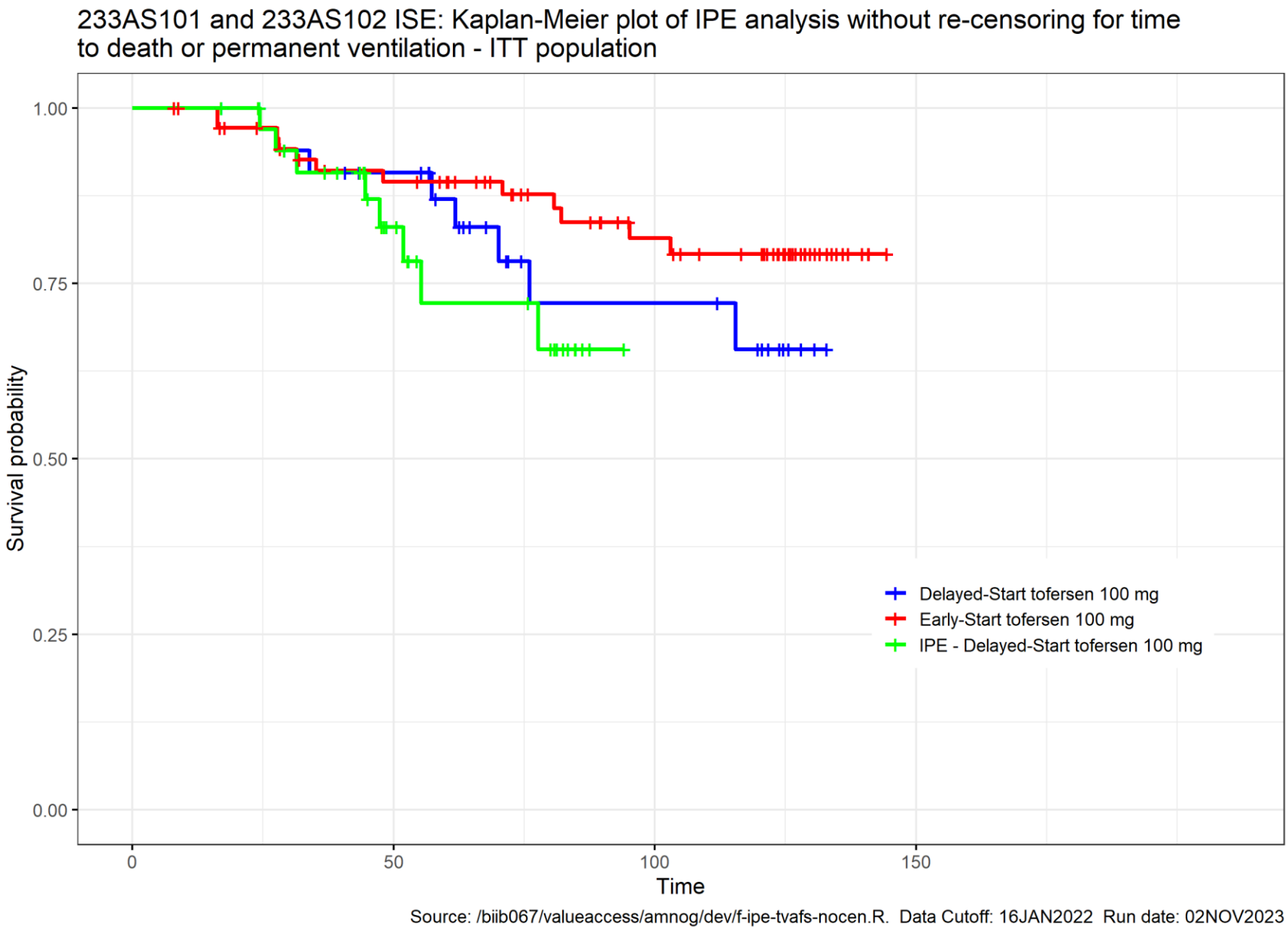
* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog4/dev/t-ipe-tvafsdp.R. Data Cutoff: 28FEB2023
Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis with re-censoring for time to death, permanent ventilation or withdrawal due to disease progression - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog4/dev/f-ipe-tvafsdp.R. Data Cutoff: 28FEB2023 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis without re-censoring for time to death or permanent ventilation - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE without re-censoring	0.24 (0.085, 0.693)	(0.063, 0.928)	0.0082	0.0089

* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
Source: /biib067/valueaccess/amnog/dev/t-ipe-tvafs-nocen.R. Data Cutoff: 16JAN2022 Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis without re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog/dev/f-ipe-tvafs-nocen.R. Data Cutoff: 16JAN2022 Run date: 02NOV2023

233AS101 and 233AS102 ISE: Summary of IPE analysis with re-censoring for time to death or permanent ventilation - ITT population

Analysis	HR from Cox (95% CI)	Adjusted Cox 95% CI*	Cox p-value	Log-rank test p-value
IPE with re-censoring	0.24 (0.077, 0.741)	(0.061, 0.927)	0.0132	0.0207

* CI constructed based on distribution of log hazard ratio retaining the Cox regression p-value from the ITT analysis, back transformed to the original scale.
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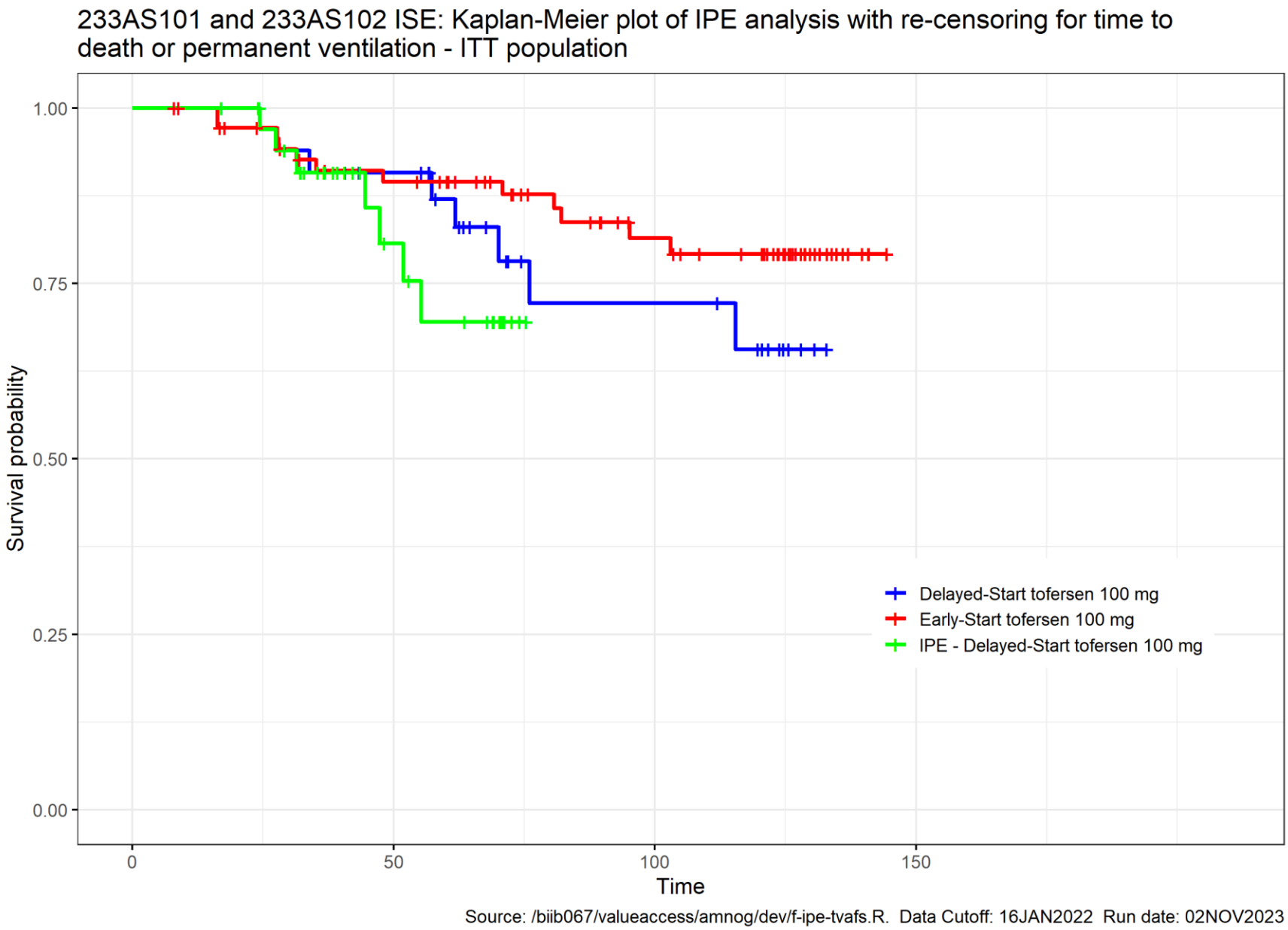
Run date: 02NOV2023


233AS101 and 233AS102 ISE: Kaplan-Meier plot of IPE analysis with re-censoring for time to death or permanent ventilation - ITT population
Survival probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Time
Delayed-Start tofersen 100 mg
Early-Start tofersen 100 mg
IPE - Delayed-Start tofersen 100 mg
Source: /biib067/valueaccess/amnog/dev/f-ipe-tvafs.R. Data Cutoff: 16JAN2022 Run date: 02NOV2023