Gemeinsamer Bundesausschuss

Tofersen (amyotrophic lateral sclerosis (ALS))

Resolution of: 19 December 2024 Valid until: unlimited
Entry into force on: 19 December 2024
Federal Gazette, BAnz AT 14.02.2024 B2

Therapeutic indication (according to the marketing authorisation of 29 May 2024):

Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

Therapeutic indication of the resolution (resolution of 19 December 2024):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Tofersen is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

Extent of the additional benefit and significance of the evidence of tofersen:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

VALOR study

- Double-blind RCT of phase III
- Comparison of **tofersen vs placebo**
- Study duration: 28 weeks (4 weeks titration plus 24 weeks stable dose treatment)

Mortality

Endpoint	Tofersen N = 72	Placebo N = 32	Tofersen vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*Hazard ratio [95% CI] p value*
Overall survival			
Deaths[a]	1 (1.4)	0 (0.0)	n.c.[b]

[1] Data from the dossier assessment of the G-BA (published on 1. Oktober 2024), and from the amendment to the dossier assessment from 29 November 2024, unless otherwise indicated.

Morbidity

Endpoint	**Tofersen N = 72**	**Placebo N = 32**	**Tofersen vs placebo**
	Patients with event n[c] (%)[d]	*Patients with event n[c] (%)[d]*	*Relative Risk [95% CI]; p value*
Motor functioning - Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R)[e]			
Bulbar domain			
Deterioration ≥ 15%	10 (14.4)	6 (16.9)	0.88 [0.35; 2.22] 0.79
Improvement ≥ 15%	0 (0.2)	4 (11.5)	0.22 [0.05; 0.91] 0.037
Fine motor skills domain			
Deterioration ≥ 15%	26 (35.5)	17 (47.4)	0.77 [0.49; 1.22] 0.27
Improvement ≥ 15%	2 (3.4)	1 (2.9)	1.15 [0.12; 11.29] 0.91
Gross motor skills domain			
Deterioration ≥ 15%	27 (37.5)	16 (44.3)	0.87 [0.54; 1.41] 0.58
Improvement ≥ 15%	3 (4.3)	1 (2.9)	1.53 [0.20; 11.74] 0.68
Respiratory domain			
Deterioration ≥ 15%	21 (29.7)	9 (25.1)	1.25 [0.64; 2.41] 0.52
Improvement ≥ 15%	3 (3.9)	3 (9.6)	0.39 [0.07; 2.13] 0.28
Total score[f] (primary endpoint; presented additionally)			
Deterioration ≥ 15%	18 (25.3)	10 (27.8)	0.95 [0.48; 1.87] 0.87
Improvement ≥ 15%	0 (0.35)	0 (0.06)	0.60 [0.13; 2.76] 0.51

Endpoint	Tofersen N = 72	Placebo N = 32	Tofersen vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*Hazard ratio [95% CI]; p value*
Time to death or permanent ventilation[a, g]			
Time to death or permanent ventilation	4 (5.6)	2 (5.6)	0.97 [0.17; 5.71]; 0.98
Time to permanent ventilation	3 (4.2)	2 (5.6)	0.82 [0.13; 5.34]; 0.83
Endpoint	**Tofersen N = 72**	**Placebo N = 32**	**Tofersen vs placebo**
	Patients with event n[c] (%)[d]	*Patients with event n[c] (%)[d]*	*Relative Risk [95% CI]; p value*
Fatigue - Fatigue Severity Scale (FSS)[h]			
Deterioration ≥ 15%	25 (34.7)	15 (40.4)	0.88 [0.51; 1.51] 0.64
Improvement ≥ 15%	9 (12.2)	4 (11.5)	1.02 [0.32; 3.24] 0.98
General health status - EuroQol Five Dimension Questionnaire - Visual Analogue Scale (EQ-5D VAS)[i]			
Deterioration ≥ 15%	19 (25.8)	13 (36.6)	0.73 [0.40; 1.33] 0.64
Improvement ≥ 15%	4 (5.4)	2 (6.0)	0.90 [0.16; 5.15] 0.91
Activities of daily living - Work Productivity and Activity Impairment Questionnaire (WPAI) item 6[j]			
Deterioration ≥ 15%	23 (31.9)	11 (31.8)	1.02 [0.56; 1.90] 0.94
Improvement ≥ 15%	10 (13.8)	4 (12.0)	1.12 [0.36; 3.51] 0.84

Health-related quality of life

Endpoint	Tofersen N = 72	Placebo N = 32	Tofersen vs placebo
	Patients with event n[c] (%)[d]	*Patients with event n[c] (%)[d]*	*Relative Risk [95% CI]; p value*
36-item Short Form Health Survey (SF-36)[k]			
Mental Component Summary (MCS) score[l]			
Deterioration ≥ 15%	12 (16.1)	8 (22.6)	0.73 [0.30; 1.75] 0.48
Improvement ≥ 15%	10 (13.8)	4 (10.4)	1.35 [0.41; 4.46] 0.63
Physical Component Summary (PCS) score[m]			
Deterioration ≥ 15%	14 (19.3)	10 (27.3)	0.75 [0.37; 1.53] 0.43
Improvement ≥ 15%	2 (3.2)	2 (5.9)	0.54 [0.08; 3.47] 0.52

Side effects

Endpoint	Tofersen[n] N = 72	Placebo[n] N = 32	Tofersen vs placebo
	Patients with event n (%)	*Patients with event n (%)*	*Relative risk [95% CI] p value*
Total adverse events (presented additionally)	69 (95.8)	34 (94.4)	-
Serious adverse events (SAE)	13 (18.1)	5 (13.9)	1.30 [0.50; 3.36] 0.59
Severe adverse events (CTCAE grade 3 or 4)	12 (16.7)	4 (11.1)	1.50 [0.520; 4.32] 0.453
Therapy discontinuation due to adverse events	n.d.	n.d.	4.56 [0.25; 82.48][o] 0.30
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)			
No statistically significant differences.			

SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)
No statistically significant differences.
Adverse events of special interest (with statistically significant difference between the treatment arms)
Adverse events of special interest were not collected.

a. Due to the low number of events, the median time to event could not be determined.
b. No effect estimator was calculated due to the low number of events.
c. Own calculations of the number of responders - as these are not reported in the dossier - based on the mean percentage of responders in the ITT population. In some cases, this does not result in a whole number of patients with event when calculated back to the ITT population. The patient numbers were rounded to whole numbers.
d. Mean percentage of subjects in relation to the ITT population at week 28, calculated on the basis of an MI model with MAR assumption
e. A higher score indicates better motor functioning.
f. A score of 0 to 48 points can be attained, with 48 points corresponding to the best motor functioning without limitations. At baseline, the total ALSFRS-R score (MV (SD)) was 36.9 (5.9) in the intervention arm and 37.3 (5.8) in the comparator arm.
g. Endpoint defined as death or permanent ventilation (≥ 22 hours/day invasive or non-invasive continuous for ≥ 21 days) (whichever occurs first).
h. A total score of 63 points can be attained. Higher scores indicate severe fatigue symptomatology. At baseline, the total FSS score (MV (SD)) was 37.1 (13.8) in the tofersen arm and 37.7 (16.3) in the placebo arm.
i. The score can range from 0 (worst perceivable health status) to 100 (best perceivable health status). At baseline, the total VAS score (MV (SD)) was 66.8 (19.6) in the intervention arm and 73.8 (16.9) in the comparator arm.
j. Higher scores indicate greater impairment. At baseline, the WPAI item 6 score (SD) was 54.2 (25.9) in the intervention arm and 47.8 (26.4) in the comparator arm.
k. Scores from 0 to 100 can be assumed, with higher scores corresponding to a higher quality of life.
l. At baseline, the MCS (MV (SD)) was 51.4 (12.31) in the intervention arm and 50.9 (10.84) in the comparator arm.
m. At baseline, the PCS (MV (SD)) was 34.4 (9.57) in the intervention arm and 36.0 (10.84) in the comparator arm.
n. Adverse events were collected from the first day of receiving study medication up to week 28 if participating or week 32 if not participating in the OLE (open-label extension) study.
o. No event figures are reported in the dossier. The effect estimator specified for the endpoint is considered adequate after internal review.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; n.d. = no data available; CI = confidence interval; MAR = Missing At Random; MCS = Mental Component Summary; MedDRA = Medical Dictionary for Regulatory Activities; MI = Multiple Imputation; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PCS = Physical Component Summary; SD = standard deviation; SAE = serious adverse event; AE = adverse event; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

Approx. 90 to 170 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Qalsody (active ingredient: tofersen) agreed upon in the

context of the marketing authorisation at the following publicly accessible link (last access: 1 November 2024):

https://www.ema.europa.eu/en/documents/product-information/qalsody-epar-product-information_en.pdf

Treatment with tofersen should only be initiated and monitored by doctors experienced in the therapy of amyotrophic lateral sclerosis.

This medicinal product was approved under "exceptional circumstances". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tofersen	€ 354,646.24

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2024

Costs for additionally required SHI services: non-quantifiable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene

– No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.