Dokumentvorlage, Version vom 16.12.2021

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Fruquintinib (FRUZAQLA®)

Takeda GmbH

Modul 4 A, Anhang 4-G

Behandlung von Patienten mit metastasierendem Kolorektalkarzinom (mCRC), die zuvor mit verfügbaren Standardtherapien, einschließlich Fluoropyrimidin-, Oxaliplatin- und Irinotecan-basierten Chemotherapien, Anti-VEGF-Arzneimitteln und Anti-EGFR- Arzneimitteln, behandelt wurden und bei denen die Erkrankung unter Behandlung mit Trifluridin/Tipiracil oder Regorafenib fortgeschritten ist, oder die diese Behandlung nicht vertragen

Zusatzanalysen

Stand: 03.06.2024

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Studie FRESCO-2, Zusatzanalysen

1. ITT-Population

1.1 Analysen Tumoransprechen

Table 35.1.1.2.1A
Objective Response Rate and Disease Control Rate based on Investigator Assessments
Intent-to-Treat Population

	Placebo + BSC N=230 n (%)	Fruquintinib + BSC N=461 n (%)	Total N=691 n (%)	Relative Risk (Fruquintinib/ Placebo) (95% CI)[a]	Odds Ratio (Fruquintinib/ Placebo) (95% CI)[b]	Difference (%) (Fruquintinib- Placebo) (95% CI)[c]	CMH Chi-Square P-value[a]
Objective Response Rate (ORR: CR+PR)	0	7 (1.5)	7 (1.0)	NE (NE, NE)	NE (NE, NE)	1.5 (0.4, 2.7)	0.059
Disease Control Rate (DCR: CR+PR+SD for at least 7 weeks)	37 (16.1)	256 (55.5)	293 (42.4)	3.447 (2.54, 4.68)	6.595 (4.43, 9.82)	39.4 (32.8, 46.0)	<.001

a. Relative risk is comparing Fruquintinib + BSC arm to Placebo + BSC arm. Relative risk and CMH chi-square p-value are calculated using a stratified Cochran-Mantel Hanzel test accounting for the randomization schedule stratification factors.
b. Odds ratio is comparing Fruquintinib + BSC arm to Placebo + BSC arm, with odds ratio >1 favors Fruquintinib + BSC arm. Odds ratio with 95% CI and p-value are calculated using a stratified logistic regression model accounting for the randomization schedule stratification factors.
c. The difference comparing Fruquintinib + BSC arm to Placebo + BSC arm. The difference and its 95% CI are calculated using the Wald method to account for the randomization schedule stratification factors.
Note: Percentages are based on the number of subjects in each group unless otherwise specified.
BSC=Best standard care; CI: Confidence interval; CR=Complete response; DCR=Disease control rate; ORR=Objective response rate; PR=Partial response; SD=Stable disease.

1.2 Analysen Allgemeiner Gesundheitszustand

1.2.1 Rücklaufquote EQ-5D VAS

Table 35.1.1.3.1A
Compliance with EQ-5D-5L Assessments Over Time
Intent-to-Treat Population

	Placebo + BSC N=230		Fruquintinib + BSC N=461	
Visit	Expected n	Received n(%)	Expected n	Received n(%)
Baseline	230	220 (95.7)	461	421 (91.3)
Cycle 2 Day 1	199	154 (77.4)	441	363 (82.3)
Cycle 3 Day 1	182	55 (30.2)	430	254 (59.1)
Cycle 4 Day 1	155	30 (19.4)	406	201 (49.5)
Cycle 5 Day 1	135	15 (11.1)	366	139 (38.0)
Cycle 6 Day 1	119	8 (6.7)	322	128 (39.8)
Cycle 7 Day 1	101	2 (2.0)	297	84 (28.3)
Cycle 8 Day 1	92	2 (2.2)	260	66 (25.4)
Cycle 9 Day 1	82	1 (1.2)	231	43 (18.6)
Cycle 10 Day 1	71	1 (1.4)	190	35 (18.4)
Cycle 11 Day 1	57	1 (1.8)	153	21 (13.7)
Cycle 12 Day 1	48	0	120	16 (13.3)
Cycle 13 Day 1	41	1 (2.4)	87	8 (9.2)
Cycle 14 Day 1	30	0	66	6 (9.1)
Cycle 15 Day 1	21	0	51	5 (9.8)
Cycle 16 Day 1	16	0	34	4 (11.8)
Cycle 17 Day 1	11	0	20	4 (20.0)
Cycle 18 Day 1	7	0	18	4 (22.2)
Cycle 19 Day 1	3	0	9	1 (11.1)
Cycle 20 Day 1	2	0	8	1 (12.5)
Post Treatment	111	109 (98.2)	206	204 (99.0)

Note: Compliance is defined as the number of forms received divided by the number of forms expected. The number of forms received is the number of patients who completed at least 1 item in each form. Number of forms expected is the number of patients in the analysis set who are alive at each timepoint.

1.2.2 Responderanalyse – Zeit bis zur 1. Verschlechterung um ≥ 15 Punkte oder Tod

Table 35.1.1.3.5A
Summary of Time to Deterioration (Including Death) of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	193 (83.9)	372 (80.7)
Number of Subjects Censored, n (%)	37 (16.1)	89 (19.3)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.28 (1.02, 1.61)	1.91 (1.84, 1.97)
Median (95% CI)	2.40 (1.97, 2.89)	4.01 (3.71, 4.60)
75% percentile (95% CI)	5.36 (4.44, 6.21)	7.33 (6.67, 7.89)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.661 (0.093)
95% CI		(0.551, 0.793)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.3.3A
Summary of Time to Deterioration of EQ-5D-5L
Intent-to-Trea Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	43.2 (36.5, 49.9)	60.5 (55.9, 65.0)
6 months	19.7 (14.0, 25.4)	33.7 (29.1, 38.3)
9 months	7.3 (3.3, 11.4)	15.3 (11.5, 19.1)
12 months	4.7 (1.4, 8.0)	7.6 (4.5, 10.8)
18 months	0.0 (NE, NE)	1.8 (0.0, 3.7)
Median Follow-up Time (months)	1.97	3.68

* indicates censored value.

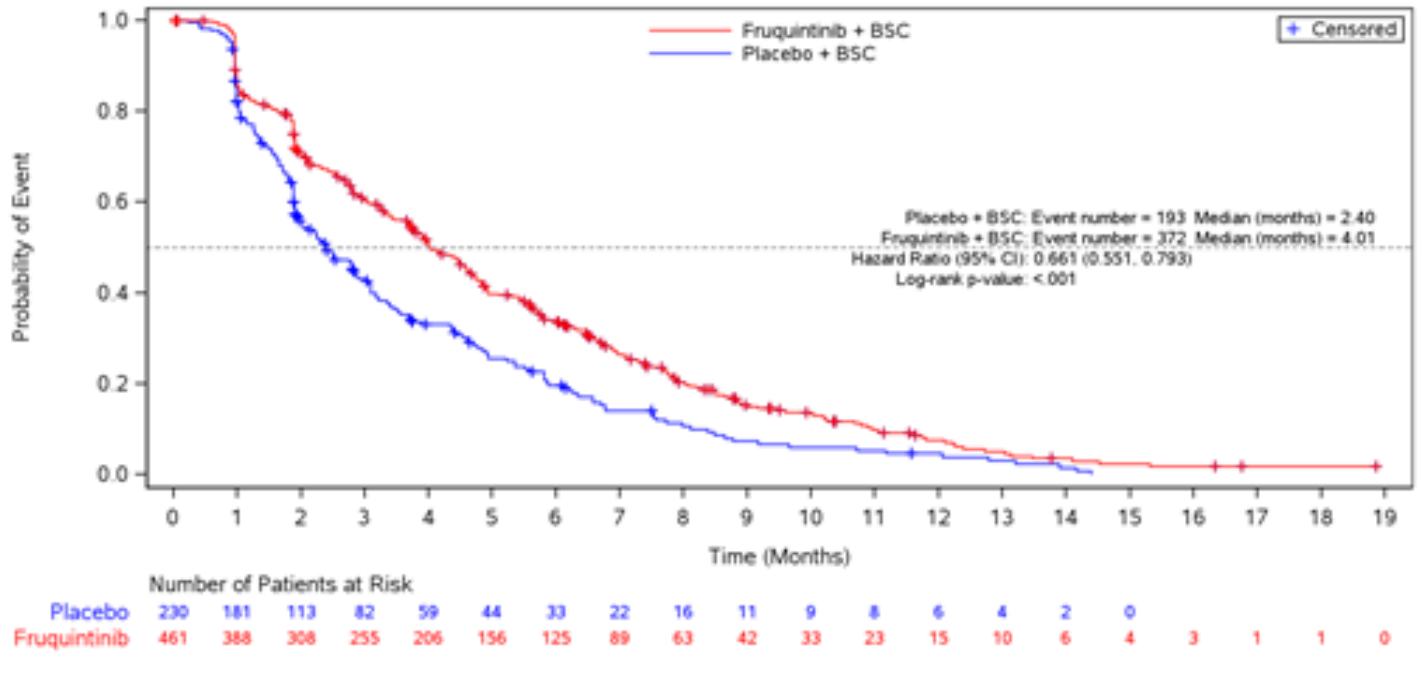
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.3.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score



BSC=Best supportive care.

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1.2.3 Responderanalyse – Zeit bis zur 1. Verschlechterung um ≥ 15 Punkte

Table 35.1.1.3.3A
Summary of Time to Deterioration of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	76 (33.0)	183 (39.7)
Number of Subjects Censored, n (%)	154 (67.0)	278 (60.3)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.41, 1.97)	1.97 (1.87, 2.76)
Median (95% CI)	NE (5.82, NE)	10.25 (6.90, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.949 (0.138)
95% CI		(0.724, 1.245)
Log-rank p-value		0.706

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.3.3A
Summary of Time to Deterioration of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	64.7 (57.9, 71.6)	67.5 (63.0, 72.0)
6 months	57.0 (48.8, 65.2)	56.4 (51.3, 61.6)
9 months	57.0 (48.8, 65.2)	50.7 (44.8, 56.5)
12 months	57.0 (48.8, 65.2)	46.1 (37.9, 54.3)
18 months	NE (NE, NE)	46.1 (37.9, 54.3)
Median Follow-up Time (months)	1.97	3.68

* indicates censored value.

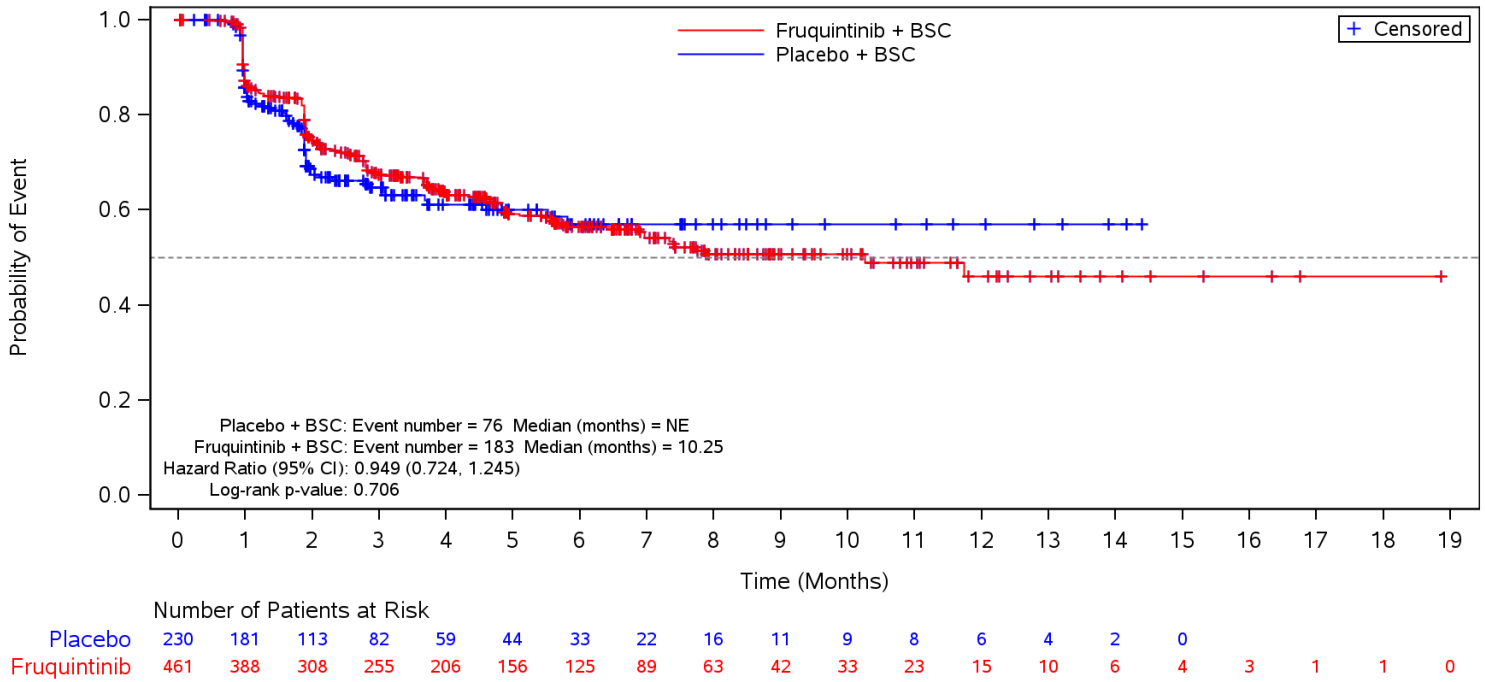
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.3.3A
Kaplan-Meier Plot for Time to Deterioration of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score



BSC=Best supportive care.

1.2.4 Responderanalyse – Zeit bis zur 1. Verbesserung um ≥ 15 Punkte

Table 35.1.1.3.4A
Summary of Time to Improvement of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	36 (15.7)	112 (24.3)
Number of Subjects Censored, n (%)	194 (84.3)	349 (75.7)
Time to Improvement (months)		
25% percentile (95% CI)	NE (4.37, NE)	4.37 (2.79, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.346 (0.193)
95% CI		(0.923, 1.963)
Log-rank p-value		0.122

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.3.4A
Summary of Time to Improvement of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	81.8 (76.2, 87.4)	78.6 (74.7, 82.5)
6 months	80.5 (74.4, 86.5)	73.8 (69.4, 78.1)
9 months	80.5 (74.4, 86.5)	70.9 (66.0, 75.9)
12 months	80.5 (74.4, 86.5)	70.9 (66.0, 75.9)
18 months	NE (NE, NE)	70.9 (66.0, 75.9)
Median Follow-up Time (months)	2.43	3.94

* indicates censored value.

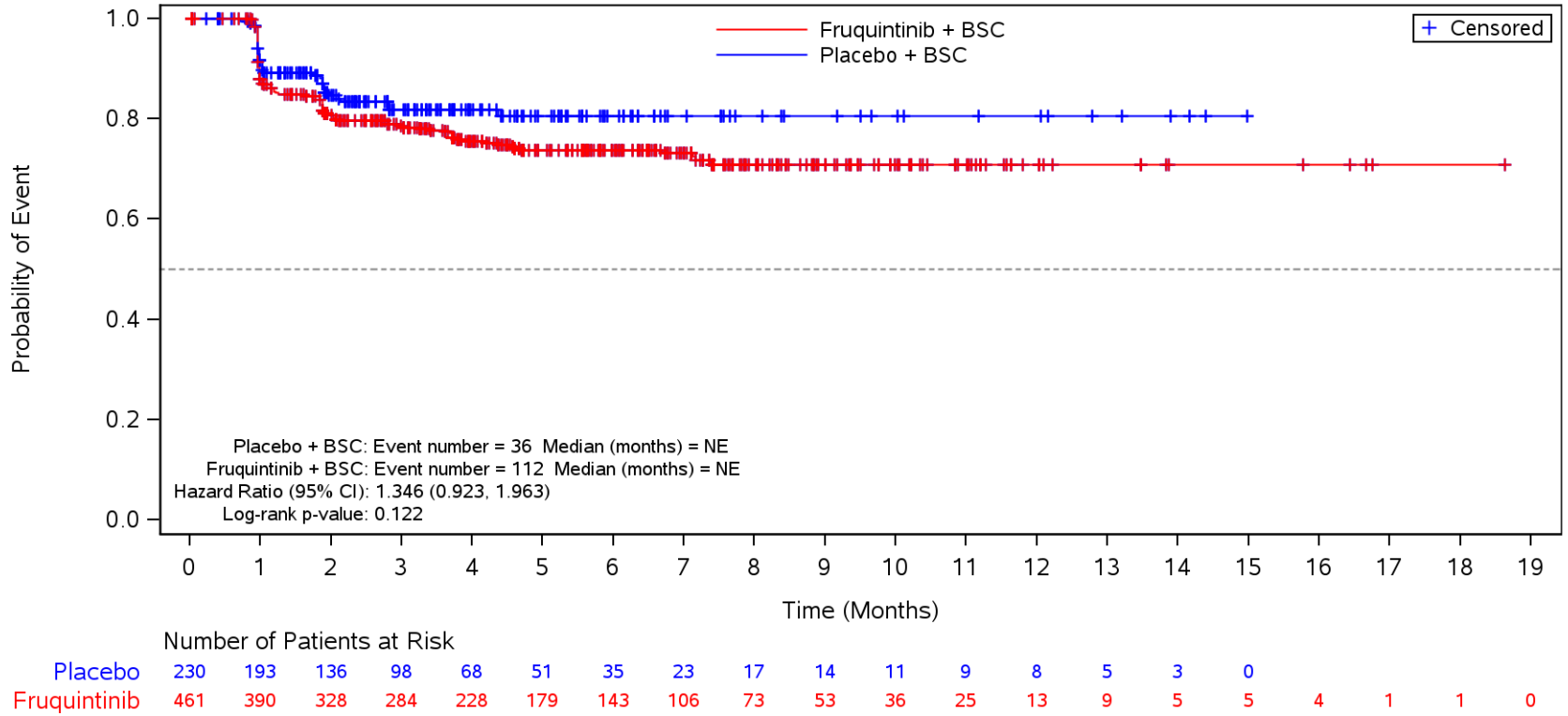
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.3.4A
Kaplan-Meier Plot for Time to Improvement of EQ-5D-5L
Intent-to-Treat Population
EQ5D02-EQ VAS Score



BSC=Best supportive care.

1.2.5 MMRM-Analyse

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	220	421
Mean (SD)	66.6 (20.30)	67.0 (18.96)
Median	70.0	70.0
Min, Max	0, 100	4, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	154	363
Mean (SD)	67.7 (18.10)	68.0 (16.49)
Median	70.0	70.0
Min, Max	20, 100	11, 100
Change from Baseline		
n	151	337
Mean (SD)	-2.0 (18.34)	0.2 (19.20)
Median	-2.0	0.0
Min, Max	-59, 60	-61, 85
LS Mean change from baseline (SE)	-0.9 (1.69)	-0.3 (1.38)
95% CI	(-4.2, 2.4)	(-3.0, 2.4)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		0.6 (1.47)
95% CI		(-2.3, 3.5)
P-value		0.675
Hedges's g		0.04 (-0.15, 0.23)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	55	254
Mean (SD)	68.4 (19.94)	68.0 (16.16)
Median	70.0	70.0
Min, Max	20, 100	10, 100
Change from Baseline		
n	54	232
Mean (SD)	-2.3 (18.57)	-0.3 (19.24)
Median	-1.0	0.0
Min, Max	-40, 58	-61, 74
LS Mean change from baseline (SE)	-2.5 (2.22)	-1.1 (1.48)
95% CI	(-6.9, 1.8)	(-4.0, 1.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.4 (2.14)
95% CI		(-2.8, 5.6)
P-value		0.514
Hedges's g		0.10 (-0.20, 0.39)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	201
Mean (SD)	71.8 (17.06)	65.8 (18.32)
Median	73.0	69.0
Min, Max	39, 95	0, 100
Change from Baseline		
n	30	185
Mean (SD)	-0.1 (15.66)	-2.9 (21.35)
Median	-0.5	-2.0
Min, Max	-36, 32	-98, 64
LS Mean change from baseline (SE)	-2.1 (2.79)	-4.0 (1.59)
95% CI	(-7.5, 3.4)	(-7.1, -0.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.0 (2.80)
95% CI		(-7.5, 3.5)
P-value		0.481
Hedges's g		-0.14 (-0.52, 0.25)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.3.2A
MMRM Analysis of EQ-5D-5L Visual Analogue Scale Over Time
Intent-to-Treat Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	151	337
LS Mean change from baseline (SE)	-0.9 (1.79)	0.1 (1.48)
95% CI	(-4.4, 2.7)	(-2.8, 3.0)
LS Mean difference (Fruquintinib – Placebo) (SE)		1.0 (1.47)
95% CI		(-1.9, 3.9)
P-value		0.500
Hedges's g		0.07 (-0.13, 0.26)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

1.3 Analysen Symptomatik und gesundheitsbezogene Lebensqualität (EORTC QLQ-C30)

1.3.1 Rücklauquote EORTC QLQ-C30

Table 35.1.1.4.1A
Compliance with EORTC QLQ-C30 V3.0 Assessments Over Time
Intent-to-Treat Population

	Placebo + BSC N=230		Fruquintinib + BSC N=461	
Visit	Expected n	Received n(%)	Expected n	Received n(%)
Baseline	230	217 (94.3)	461	420 (91.1)
Cycle 2 Day 1	199	153 (76.9)	441	357 (81.0)
Cycle 3 Day 1	182	53 (29.1)	431	253 (58.7)
Cycle 4 Day 1	155	30 (19.4)	406	200 (49.3)
Cycle 5 Day 1	135	15 (11.1)	366	137 (37.4)
Cycle 6 Day 1	119	8 (6.7)	322	128 (39.8)
Cycle 7 Day 1	101	2 (2.0)	297	82 (27.6)
Cycle 8 Day 1	92	2 (2.2)	261	65 (24.9)
Cycle 9 Day 1	82	1 (1.2)	231	42 (18.2)
Cycle 10 Day 1	70	1 (1.4)	190	35 (18.4)
Cycle 11 Day 1	57	1 (1.8)	153	21 (13.7)
Cycle 12 Day 1	48	0	120	16 (13.3)
Cycle 13 Day 1	41	1 (2.4)	87	8 (9.2)
Cycle 14 Day 1	30	0	66	6 (9.1)
Cycle 15 Day 1	19	0	51	5 (9.8)
Cycle 16 Day 1	16	0	34	4 (11.8)
Cycle 17 Day 1	11	0	20	4 (20.0)
Cycle 18 Day 1	7	0	18	4 (22.2)
Cycle 19 Day 1	3	0	9	1 (11.1)
Cycle 20 Day 1	2	0	8	1 (12.5)
Post Treatment	108	107 (99.1)	206	205 (99.5)

Note: Compliance is defined as the number of forms received divided by the number of forms expected. The number of forms received is the number of patients who completed at least 1 item in each form. Number of forms expected is the number of patients in the analysis set who are alive at each timepoint.

1.3.2 Responderanalyse – Zeit bis zur 1. Verschlechterung um ≥ 10 Punkte oder Tod

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	198 (86.1)	395 (85.7)
Number of Subjects Censored, n (%)	32 (13.9)	66 (14.3)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	0.99 (0.95, 1.08)	1.15 (0.99, 1.64)
Median (95% CI)	1.91 (1.84, 2.10)	2.79 (2.23, 3.25)
75% percentile (95% CI)	4.34 (3.19, 5.52)	5.75 (4.93, 6.31)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.746 (0.090)
95% CI		(0.625, 0.891)
Log-rank p-value		0.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	33.2 (26.8, 39.7)	47.1 (42.4, 51.7)
6 months	15.7 (10.4, 21.0)	23.6 (19.5, 27.6)
9 months	6.3 (2.6, 10.0)	10.7 (7.4, 13.9)
12 months	3.8 (0.8, 6.7)	3.9 (1.5, 6.4)
18 months	0.0 (NE, NE)	1.3 (0.0, 2.9)
Median Follow-up Time (months)	1.87	2.43

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	188 (81.7)	401 (87.0)
Number of Subjects Censored, n (%)	42 (18.3)	60 (13.0)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.05 (0.99, 1.28)	1.15 (0.99, 1.64)
Median (95% CI)	1.97 (1.87, 2.40)	2.76 (2.30, 2.89)
75% percentile (95% CI)	5.36 (4.34, 6.57)	5.55 (4.86, 6.47)
Min, Max	0.0*, 14.4	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.858 (0.092)
95% CI		(0.717, 1.027)
Log-rank p-value		0.095

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	37.5 (30.9, 44.2)	44.1 (39.4, 48.7)
6 months	20.8 (14.8, 26.8)	22.4 (18.4, 26.5)
9 months	8.2 (3.7, 12.6)	9.5 (6.4, 12.5)
12 months	5.2 (1.5, 8.9)	5.2 (2.6, 7.8)
18 months	0.0 (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	2.37

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	193 (83.9)	405 (87.9)
Number of Subjects Censored, n (%)	37 (16.1)	56 (12.1)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.02 (0.99, 1.22)	0.99 (0.99, 1.05)
Median (95% CI)	1.94 (1.84, 2.23)	2.33 (1.91, 2.79)
75% percentile (95% CI)	4.40 (3.19, 5.13)	5.36 (4.57, 6.11)
Min, Max	0.0*, 14.4	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.811 (0.091)
95% CI		(0.679, 0.970)
Log-rank p-value		0.022

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	33.5 (27.0, 40.0)	41.8 (37.2, 46.4)
6 months	15.5 (10.2, 20.9)	21.8 (17.8, 25.8)
9 months	4.9 (1.5, 8.4)	7.4 (4.6, 10.2)
12 months	2.1 (0.0, 4.5)	2.5 (0.6, 4.4)
18 months	0.0 (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	2.04

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	191 (83.0)	379 (82.2)
Number of Subjects Censored, n (%)	39 (17.0)	82 (17.8)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.41 (1.22, 1.74)	1.91 (1.87, 1.97)
Median (95% CI)	2.63 (2.17, 3.09)	3.88 (3.61, 4.30)
75% percentile (95% CI)	5.16 (4.37, 6.14)	6.67 (6.24, 7.26)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.699 (0.092)
95% CI		(0.583, 0.837)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	44.0 (37.2, 50.8)	59.0 (54.4, 63.6)
6 months	19.9 (14.1, 25.7)	30.8 (26.4, 35.3)
9 months	7.4 (3.3, 11.5)	13.5 (9.9, 17.1)
12 months	4.0 (0.9, 7.2)	5.7 (2.9, 8.6)
18 months	0.0 (NE, NE)	1.5 (0.0, 3.4)
Median Follow-up Time (months)	2.10	3.65

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	189 (82.2)	398 (86.3)
Number of Subjects Censored, n (%)	41 (17.8)	63 (13.7)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.22 (1.02, 1.51)	1.77 (1.12, 1.87)
Median (95% CI)	2.33 (2.00, 2.86)	2.83 (2.76, 3.35)
75% percentile (95% CI)	5.36 (4.37, 6.34)	5.62 (4.86, 6.08)
Min, Max	0.0*, 14.4	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.841 (0.091)
95% CI		(0.704, 1.005)
Log-rank p-value		0.057

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	41.9 (35.2, 48.7)	48.0 (43.4, 52.7)
6 months	22.0 (16.0, 28.0)	21.8 (17.8, 25.8)
9 months	7.2 (3.1, 11.4)	8.4 (5.4, 11.3)
12 months	2.9 (0.1, 5.6)	3.4 (1.2, 5.5)
18 months	0.0 (NE, NE)	1.3 (0.0, 2.8)
Median Follow-up Time (months)	1.94	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	189 (82.2)	391 (84.8)
Number of Subjects Censored, n (%)	41 (17.8)	70 (15.2)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.28 (1.02, 1.61)	1.45 (1.05, 1.87)
Median (95% CI)	2.20 (1.91, 2.50)	3.02 (2.79, 3.78)
75% percentile (95% CI)	4.63 (3.68, 5.88)	6.51 (5.72, 7.00)
Min, Max	0.0*, 15.0	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.746 (0.092)
95% CI		(0.623, 0.894)
Log-rank p-value		0.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	37.9 (31.2, 44.5)	50.0 (45.4, 54.7)
6 months	18.4 (12.7, 24.1)	27.5 (23.2, 31.9)
9 months	6.8 (2.7, 10.8)	11.6 (8.3, 15.0)
12 months	4.5 (1.1, 7.9)	4.6 (2.1, 7.0)
18 months	0.0 (NE, NE)	1.7 (0.0, 3.4)
Median Follow-up Time (months)	1.91	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	204 (88.7)	414 (89.8)
Number of Subjects Censored, n (%)	26 (11.3)	47 (10.2)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	0.99 (0.95, 0.99)	0.99 (0.95, 0.99)
Median (95% CI)	1.68 (1.31, 1.87)	1.91 (1.87, 2.00)
75% percentile (95% CI)	2.86 (2.40, 3.75)	4.57 (3.98, 4.93)
Min, Max	0.0*, 14.4	0.0*, 16.7
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.736 (0.089)
95% CI		(0.619, 0.876)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	24.3 (18.5, 30.2)	34.3 (29.8, 38.7)
6 months	8.5 (4.4, 12.5)	17.6 (14.0, 21.2)
9 months	4.2 (1.1, 7.4)	7.1 (4.4, 9.8)
12 months	2.8 (0.2, 5.5)	2.6 (0.7, 4.5)
18 months	0.0 (NE, NE)	0.0 (NE, NE)
Median Follow-up Time (months)	1.56	1.87

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	189 (82.2)	376 (81.6)
Number of Subjects Censored, n (%)	41 (17.8)	85 (18.4)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.51 (1.08, 1.81)	1.94 (1.87, 2.14)
Median (95% CI)	2.83 (2.27, 3.35)	4.21 (3.81, 4.63)
75% percentile (95% CI)	5.36 (4.67, 6.21)	7.56 (6.83, 8.21)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.645 (0.093)
95% CI		(0.538, 0.774)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	47.0 (40.1, 53.8)	62.0 (57.4, 66.5)
6 months	20.8 (14.9, 26.7)	35.1 (30.5, 39.7)
9 months	8.1 (3.8, 12.3)	15.9 (12.0, 19.7)
12 months	4.0 (0.9, 7.2)	6.7 (3.8, 9.6)
18 months	0.0 (NE, NE)	2.0 (0.1, 3.8)
Median Follow-up Time (months)	2.18	3.75

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	198 (86.1)	412 (89.4)
Number of Subjects Censored, n (%)	32 (13.9)	49 (10.6)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	0.99 (0.95, 1.05)	0.99 (0.95, 0.99)
Median (95% CI)	1.91 (1.71, 2.20)	1.97 (1.87, 2.56)
75% percentile (95% CI)	4.34 (3.42, 5.22)	4.80 (4.01, 5.36)
Min, Max	0.0*, 14.4	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.867 (0.089)
95% CI		(0.728, 1.033)
Log-rank p-value		0.110

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	35.6 (29.1, 42.2)	38.1 (33.5, 42.6)
6 months	13.1 (8.2, 18.1)	18.0 (14.3, 21.7)
9 months	3.8 (0.9, 6.7)	6.1 (3.6, 8.7)
12 months	1.9 (0.0, 4.0)	2.1 (0.4, 3.8)
18 months	0.0 (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	1.91

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	191 (83.0)	379 (82.2)
Number of Subjects Censored, n (%)	39 (17.0)	82 (17.8)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.15 (0.99, 1.45)	1.87 (1.61, 1.91)
Median (95% CI)	2.10 (1.91, 2.40)	4.01 (3.71, 4.57)
75% percentile (95% CI)	4.60 (3.75, 5.22)	7.59 (6.74, 8.31)
Min, Max	0.0*, 14.4	0.0*, 16.7
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.556 (0.094)
95% CI		(0.463, 0.668)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	38.8 (32.1, 45.5)	61.1 (56.6, 65.7)
6 months	13.4 (8.3, 18.6)	33.8 (29.3, 38.4)
9 months	5.0 (1.5, 8.4)	16.5 (12.7, 20.4)
12 months	2.8 (0.1, 5.5)	6.9 (3.8, 9.9)
18 months	0.0 (NE, NE)	0.0 (NE, NE)
Median Follow-up Time (months)	1.91	3.71

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	189 (82.2)	378 (82.0)
Number of Subjects Censored, n (%)	41 (17.8)	83 (18.0)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.22 (0.99, 1.41)	1.87 (1.84, 1.94)
Median (95% CI)	2.04 (1.87, 2.46)	3.81 (3.22, 4.11)
75% percentile (95% CI)	4.90 (3.88, 5.82)	7.00 (6.47, 7.75)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.600 (0.093)
95% CI		(0.500, 0.721)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	38.7 (32.0, 45.4)	57.0 (52.4, 61.6)
6 months	17.4 (11.7, 23.0)	32.4 (27.9, 36.9)
9 months	6.5 (2.5, 10.5)	14.5 (10.8, 18.3)
12 months	2.9 (0.1, 5.7)	5.8 (3.0, 8.6)
18 months	0.0 (NE, NE)	1.3 (0.0, 2.8)
Median Follow-up Time (months)	1.91	3.25

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	188 (81.7)	392 (85.0)
Number of Subjects Censored, n (%)	42 (18.3)	69 (15.0)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.28 (1.02, 1.61)	1.58 (1.08, 1.87)
Median (95% CI)	2.37 (1.94, 2.83)	3.02 (2.79, 3.71)
75% percentile (95% CI)	4.70 (3.84, 5.59)	5.88 (5.32, 6.51)
Min, Max	0.0*, 14.4	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.809 (0.093)
95% CI		(0.674, 0.971)
Log-rank p-value		0.022

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	40.6 (33.8, 47.5)	50.2 (45.5, 54.8)
6 months	17.2 (11.6, 22.9)	24.5 (20.3, 28.7)
9 months	7.6 (3.4, 11.8)	9.7 (6.5, 12.8)
12 months	4.1 (1.0, 7.3)	3.3 (1.0, 5.6)
18 months	0.0 (NE, NE)	0.6 (0.0, 1.6)
Median Follow-up Time (months)	1.91	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	187 (81.3)	371 (80.5)
Number of Subjects Censored, n (%)	43 (18.7)	90 (19.5)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.51 (1.05, 1.87)	1.91 (1.87, 2.23)
Median (95% CI)	2.83 (2.40, 3.42)	4.30 (3.91, 4.70)
75% percentile (95% CI)	5.36 (4.60, 6.24)	7.43 (6.70, 8.08)
Min, Max	0.0*, 14.4	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.645 (0.093)
95% CI		(0.537, 0.774)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	48.6 (41.8, 55.4)	62.8 (58.3, 67.3)
6 months	20.9 (14.9, 26.8)	35.2 (30.6, 39.9)
9 months	6.4 (2.5, 10.3)	15.3 (11.4, 19.1)
12 months	2.8 (0.1, 5.5)	7.5 (4.4, 10.7)
18 months	0.0 (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.28	3.84

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	183 (79.6)	380 (82.4)
Number of Subjects Censored, n (%)	47 (20.4)	81 (17.6)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.81 (1.54, 2.10)	1.94 (1.87, 2.23)
Median (95% CI)	3.29 (2.79, 3.91)	4.04 (3.75, 4.50)
75% percentile (95% CI)	5.88 (5.16, 6.57)	7.10 (6.51, 7.69)
Min, Max	0.0*, 15.0	0.0*, 16.7
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.800 (0.093)
95% CI		(0.666, 0.960)
Log-rank p-value		0.016

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	54.4 (47.5, 61.2)	63.3 (58.9, 67.8)
6 months	23.8 (17.5, 30.1)	33.9 (29.3, 38.4)
9 months	7.9 (3.7, 12.2)	14.8 (11.0, 18.5)
12 months	4.0 (0.9, 7.1)	4.2 (1.7, 6.7)
18 months	0.0 (NE, NE)	0.0 (NE, NE)
Median Follow-up Time (months)	2.51	3.75

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	182 (79.1)	362 (78.5)
Number of Subjects Censored, n (%)	48 (20.9)	99 (21.5)
Time to Deterioration (Including Death) (months)		
25% percentile (95% CI)	1.61 (1.25, 1.87)	2.50 (2.07, 2.79)
Median (95% CI)	2.86 (2.46, 3.68)	4.90 (4.50, 5.65)
75% percentile (95% CI)	5.59 (4.93, 6.74)	8.31 (7.69, 9.13)
Min, Max	0.0*, 15.0	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.601 (0.095)
95% CI		(0.500, 0.724)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.5A
Summary of Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	49.2 (42.3, 56.1)	68.9 (64.6, 73.2)
6 months	22.8 (16.6, 29.1)	42.3 (37.5, 47.1)
9 months	9.8 (5.1, 14.5)	21.0 (16.7, 25.2)
12 months	5.6 (1.9, 9.3)	9.3 (5.9, 12.7)
18 months	0.0 (NE, NE)	0.8 (0.0, 2.1)
Median Follow-up Time (months)	2.35	4.30

* indicates censored value.

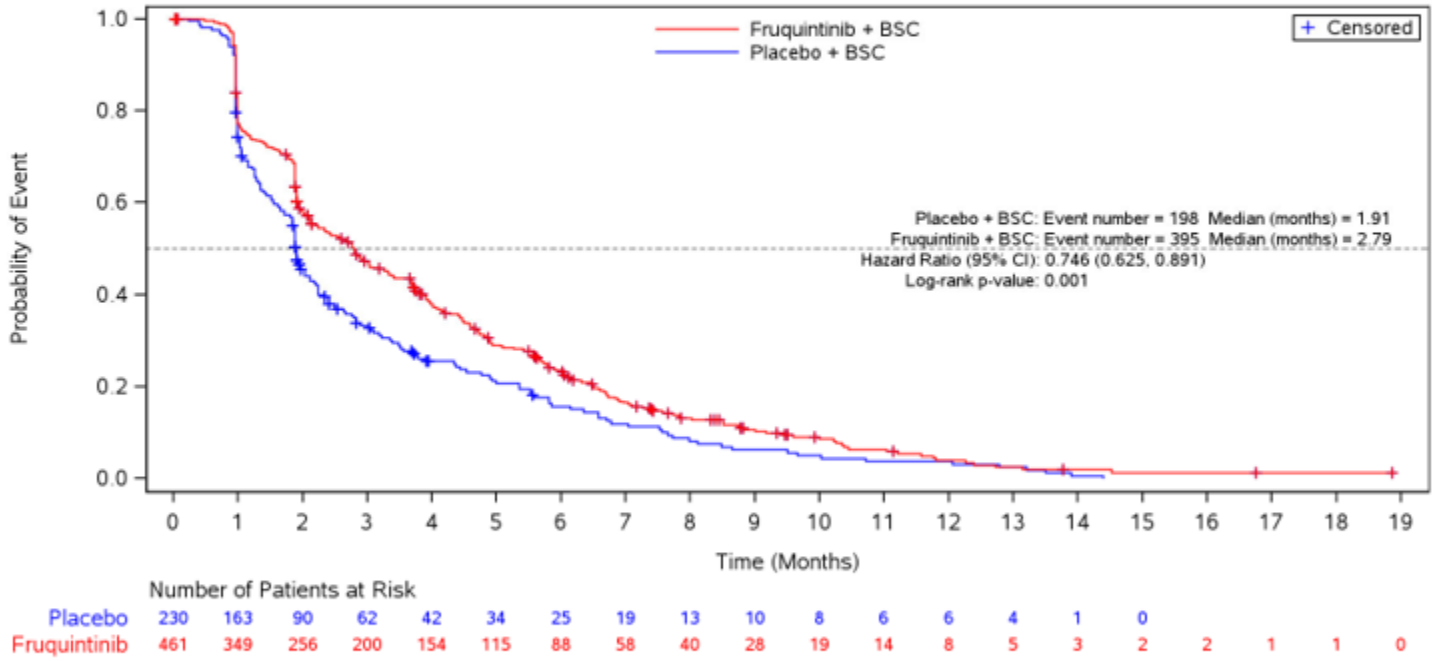
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (last date of observed measurement – randomization date + 1)/30.4375.

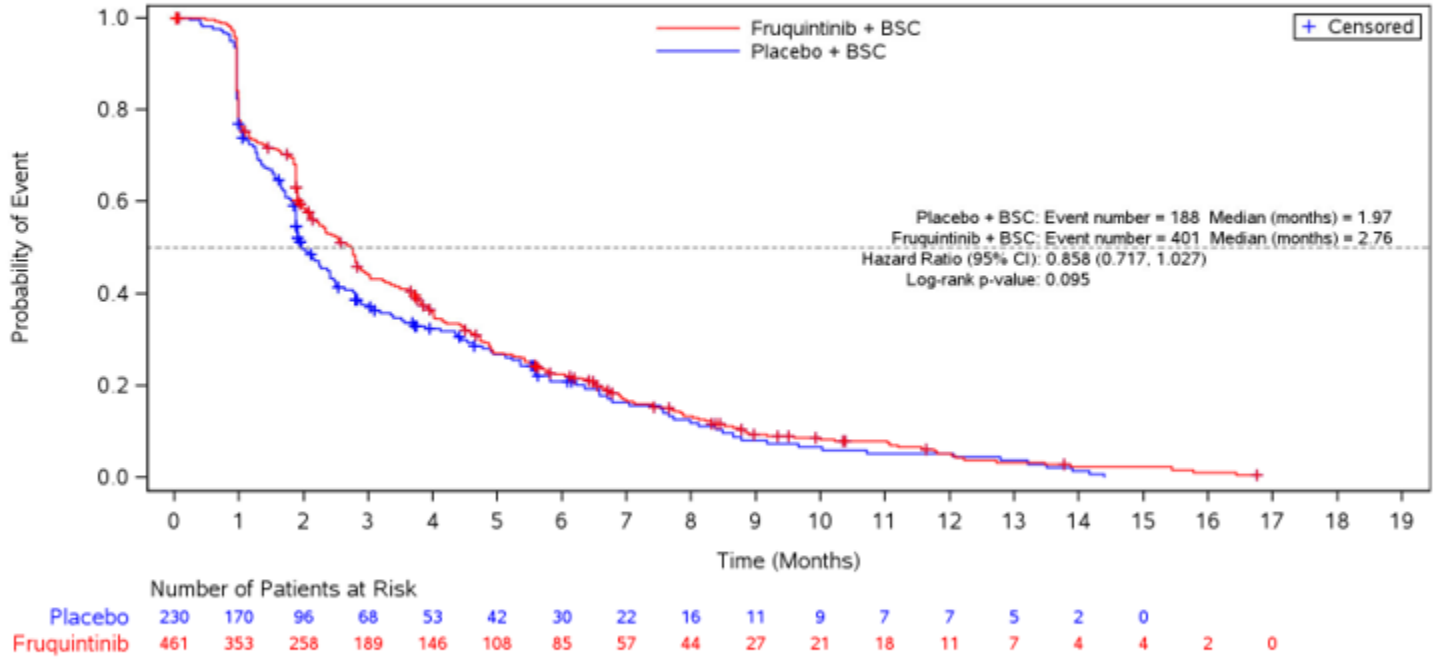
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL



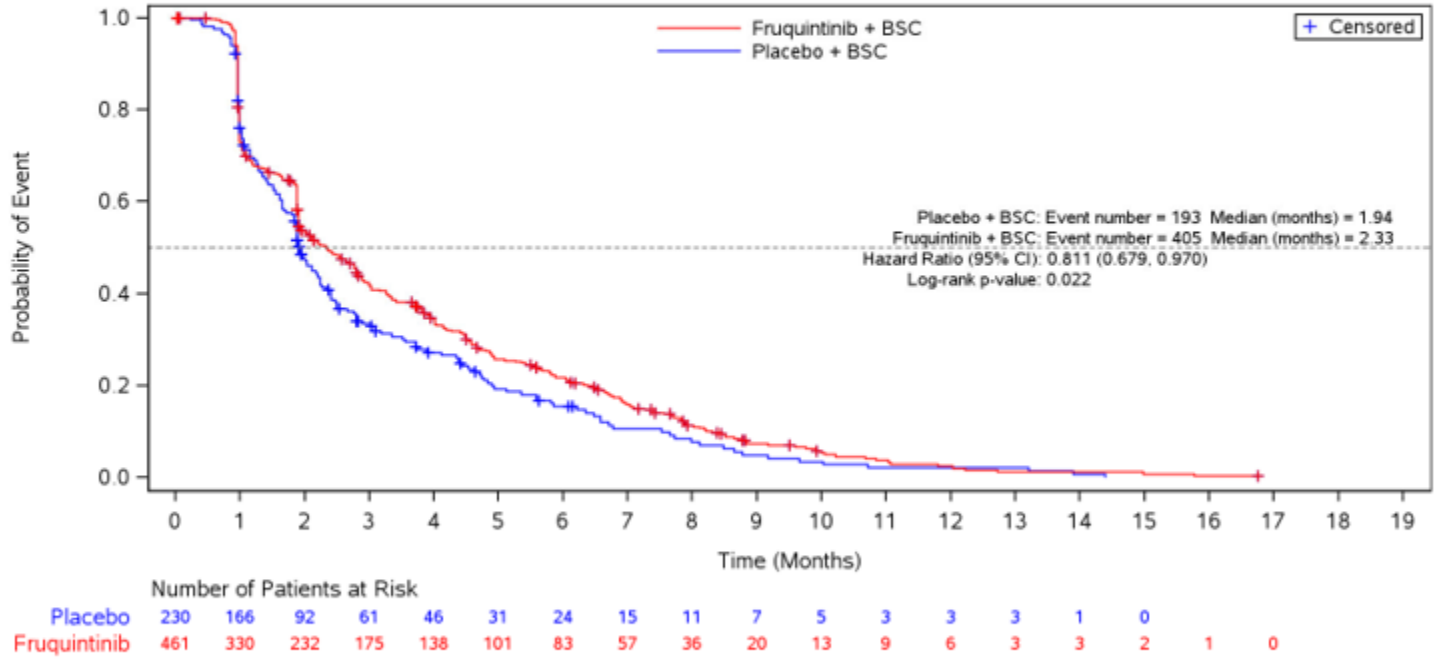
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning



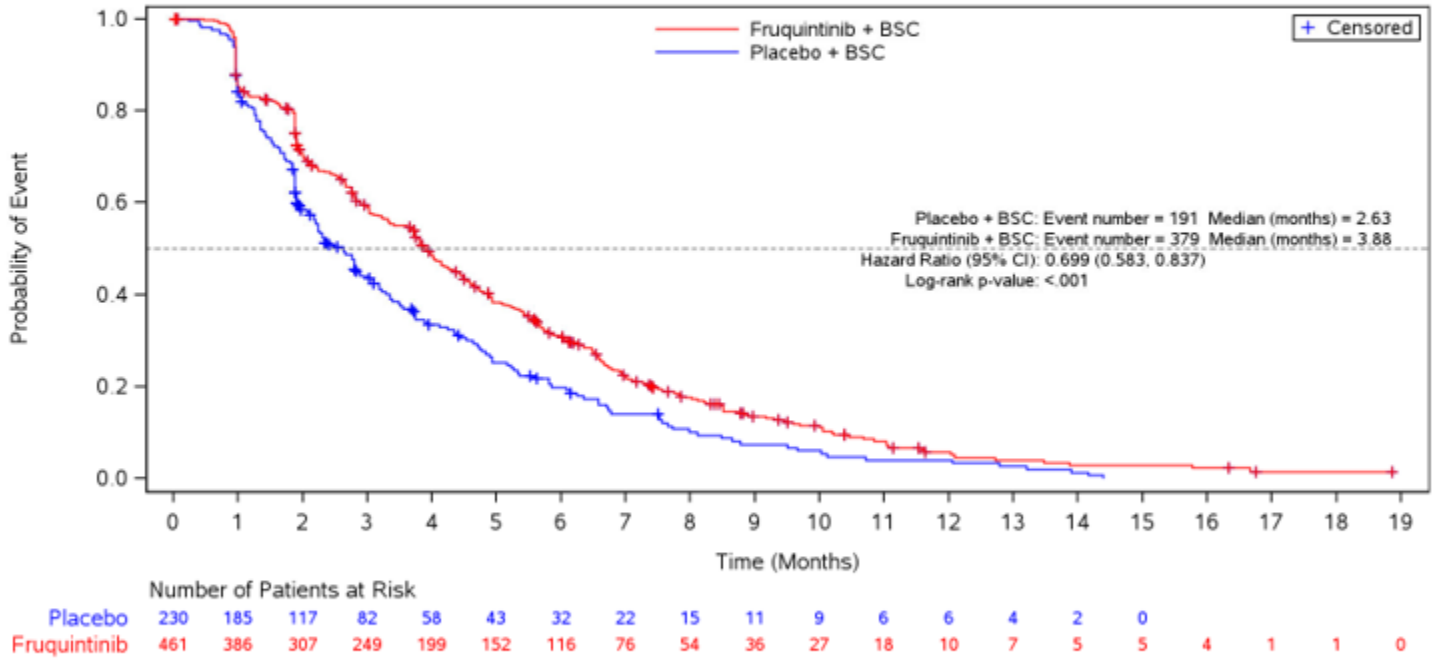
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning



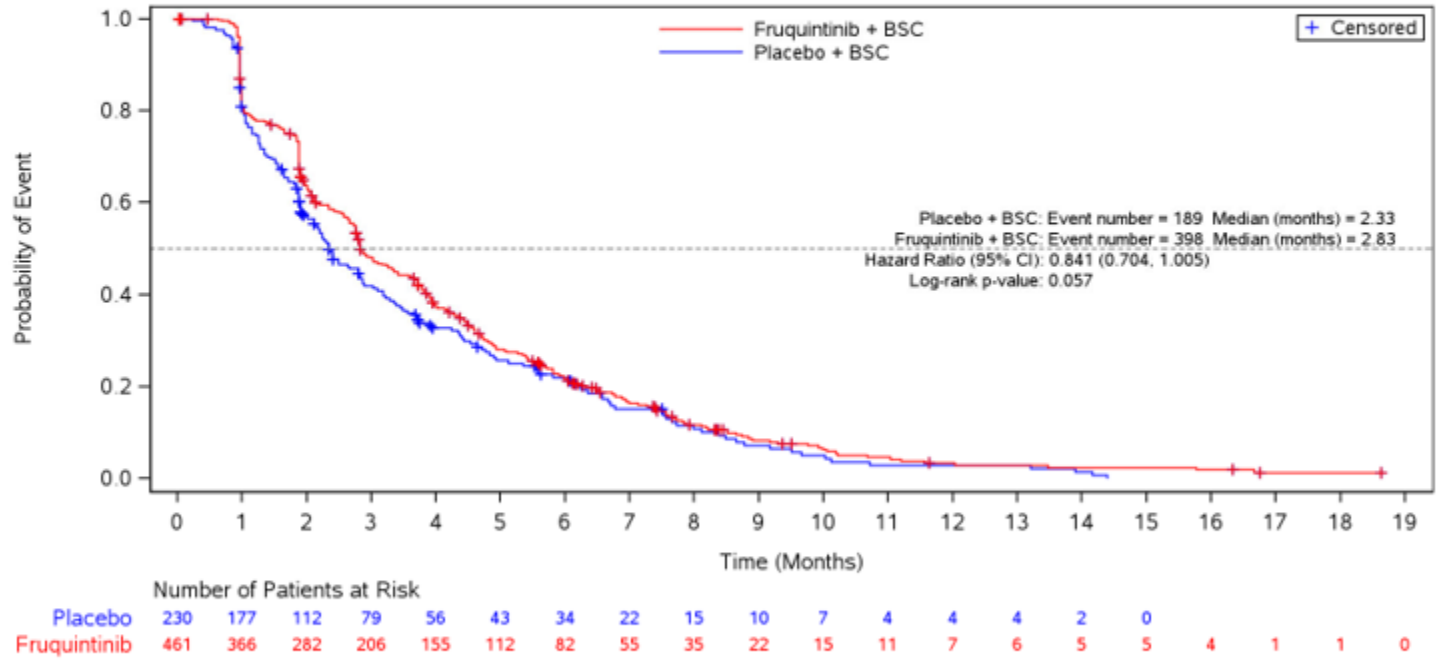
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning



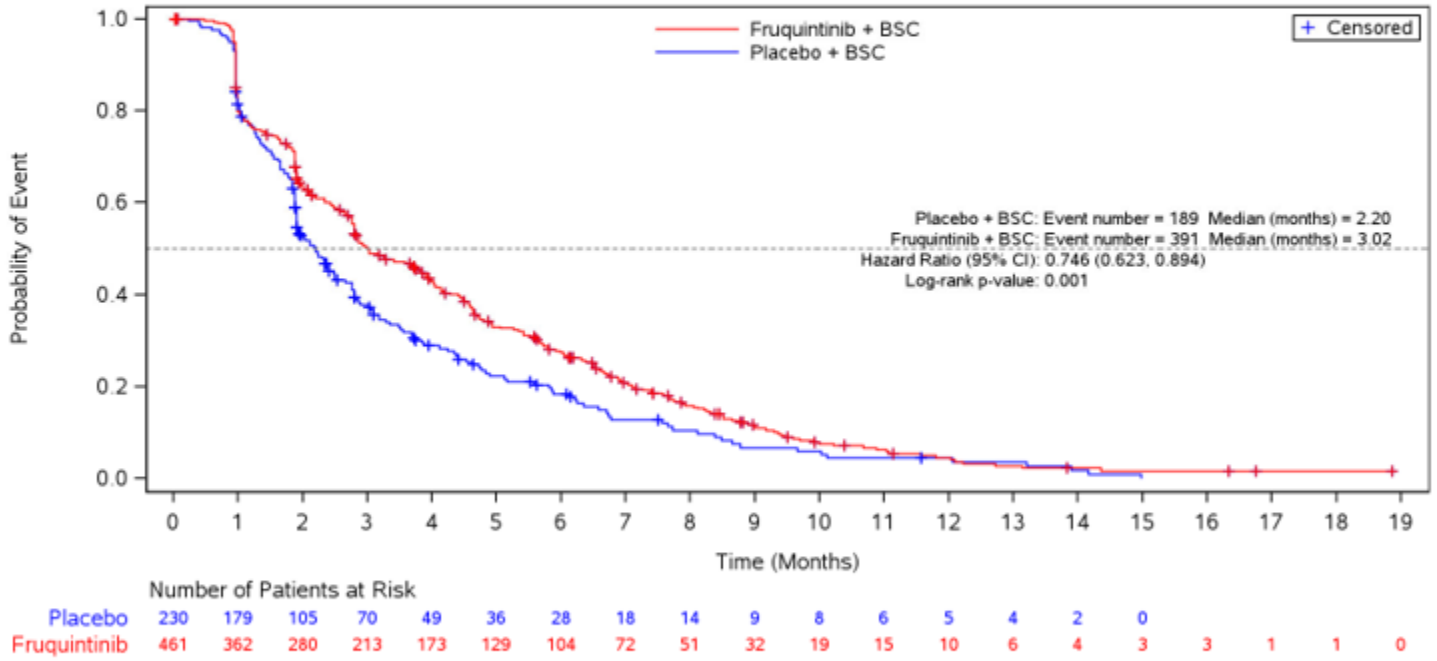
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning



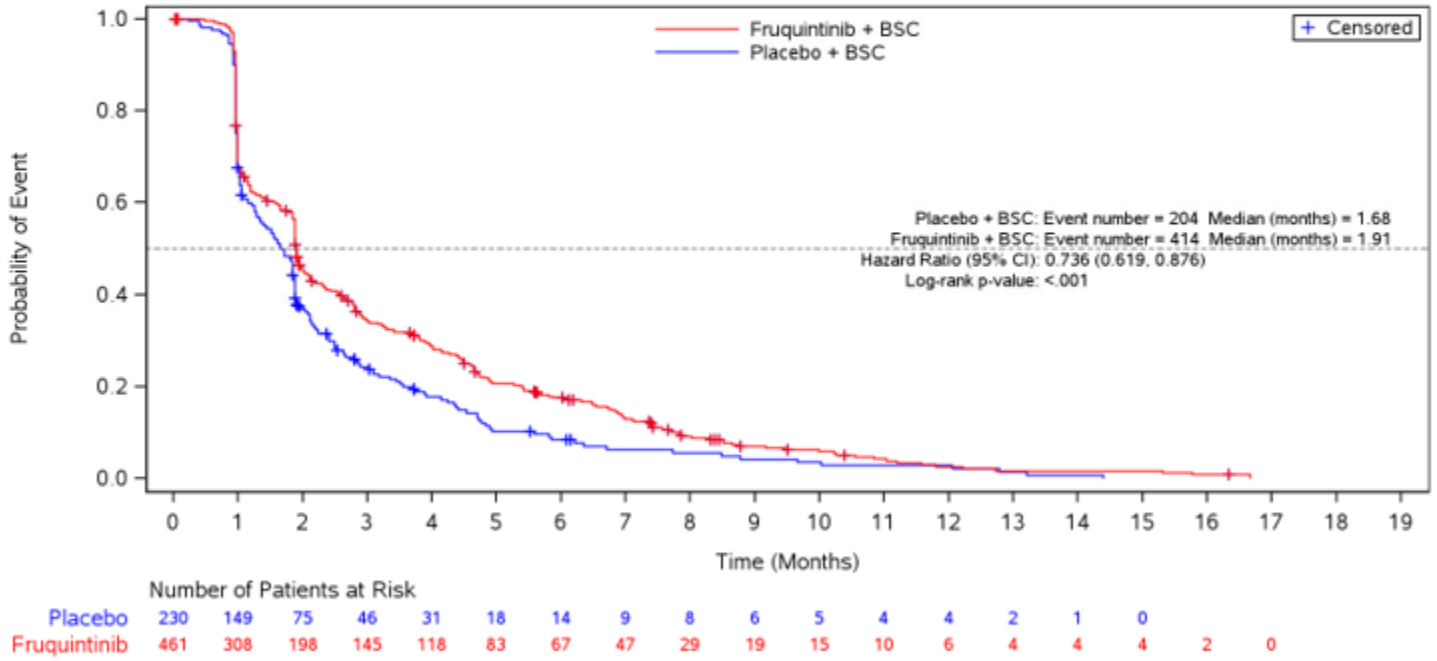
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning



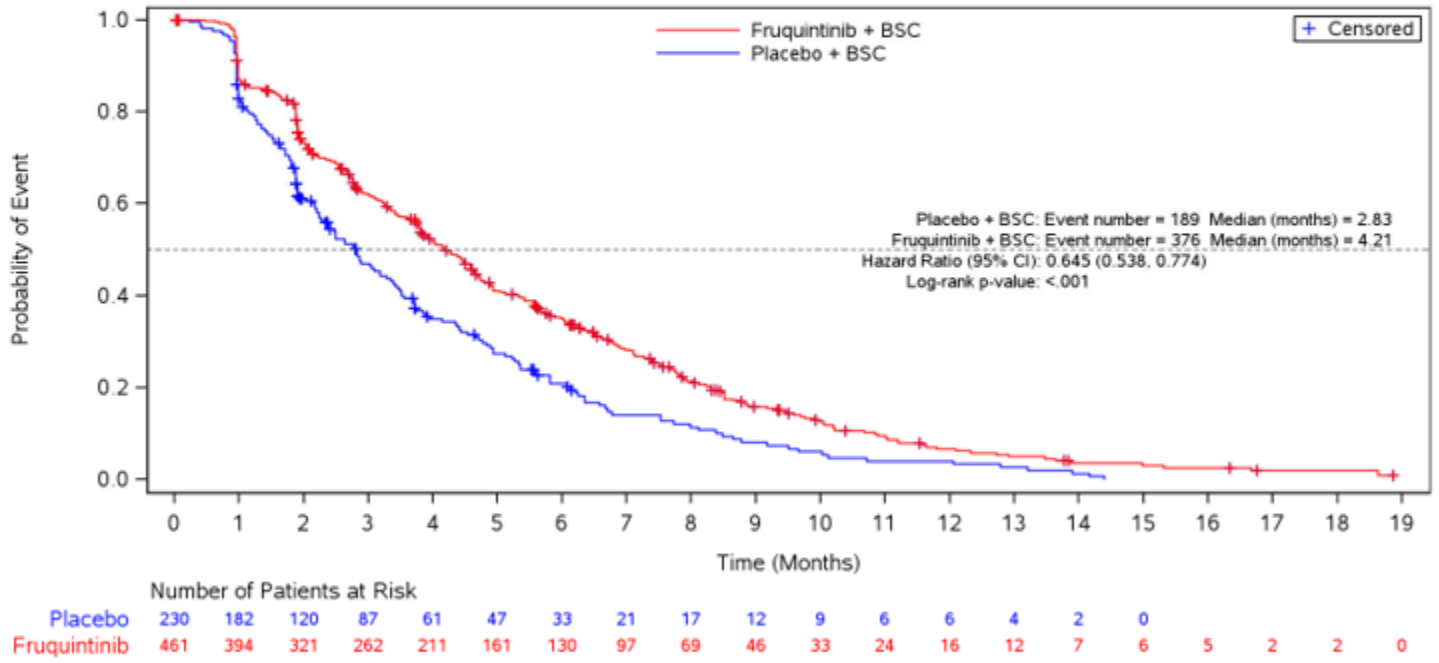
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue



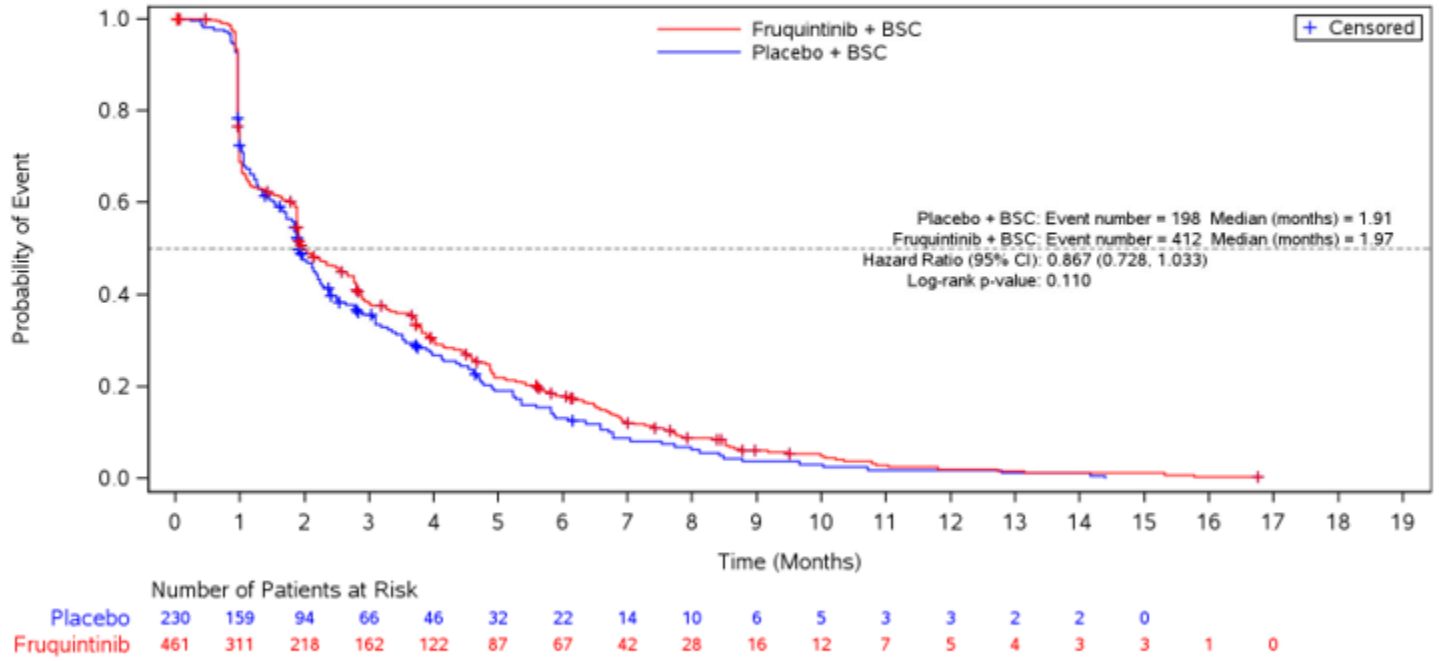
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting



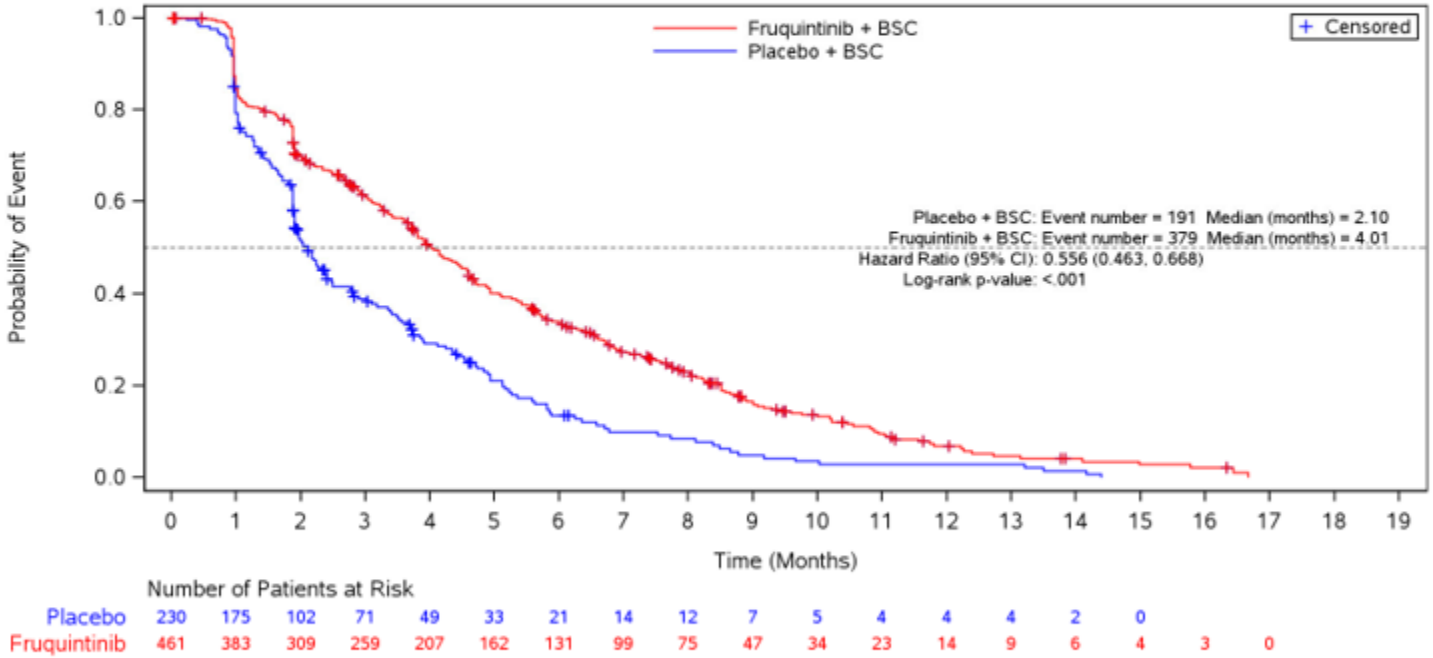
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain



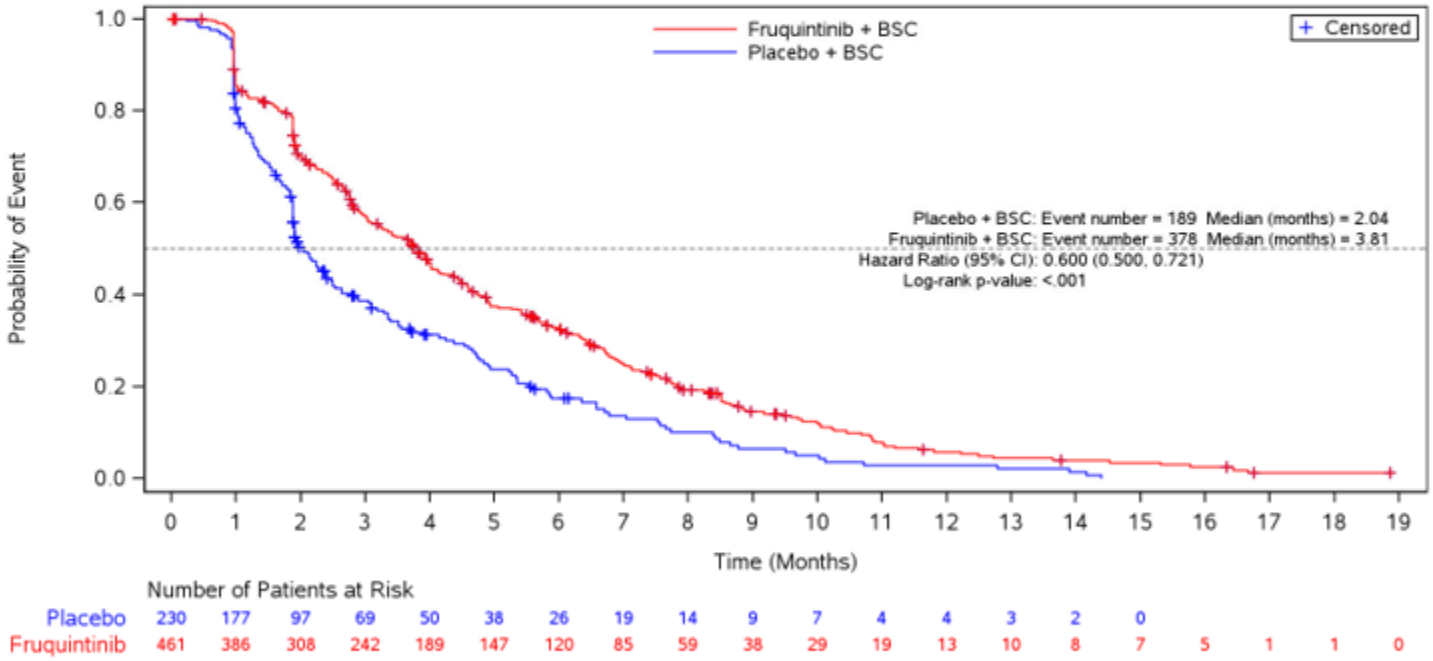
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea



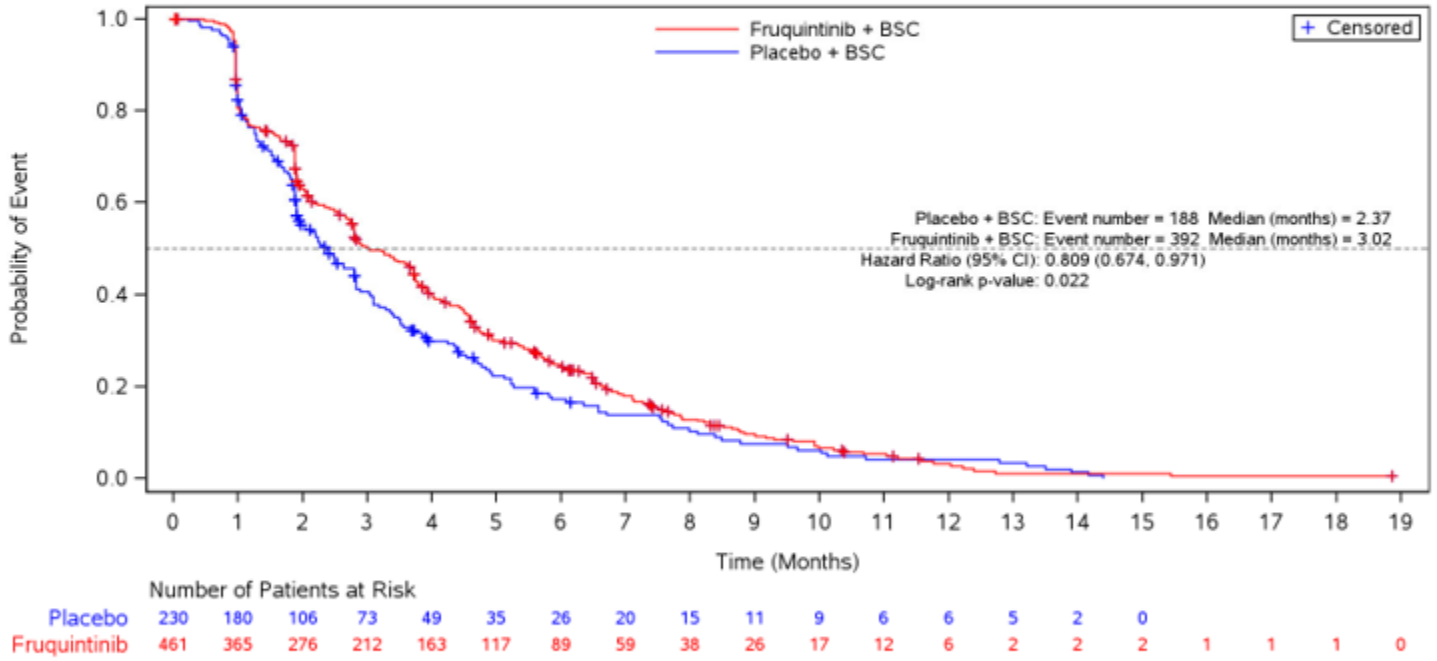
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia



BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

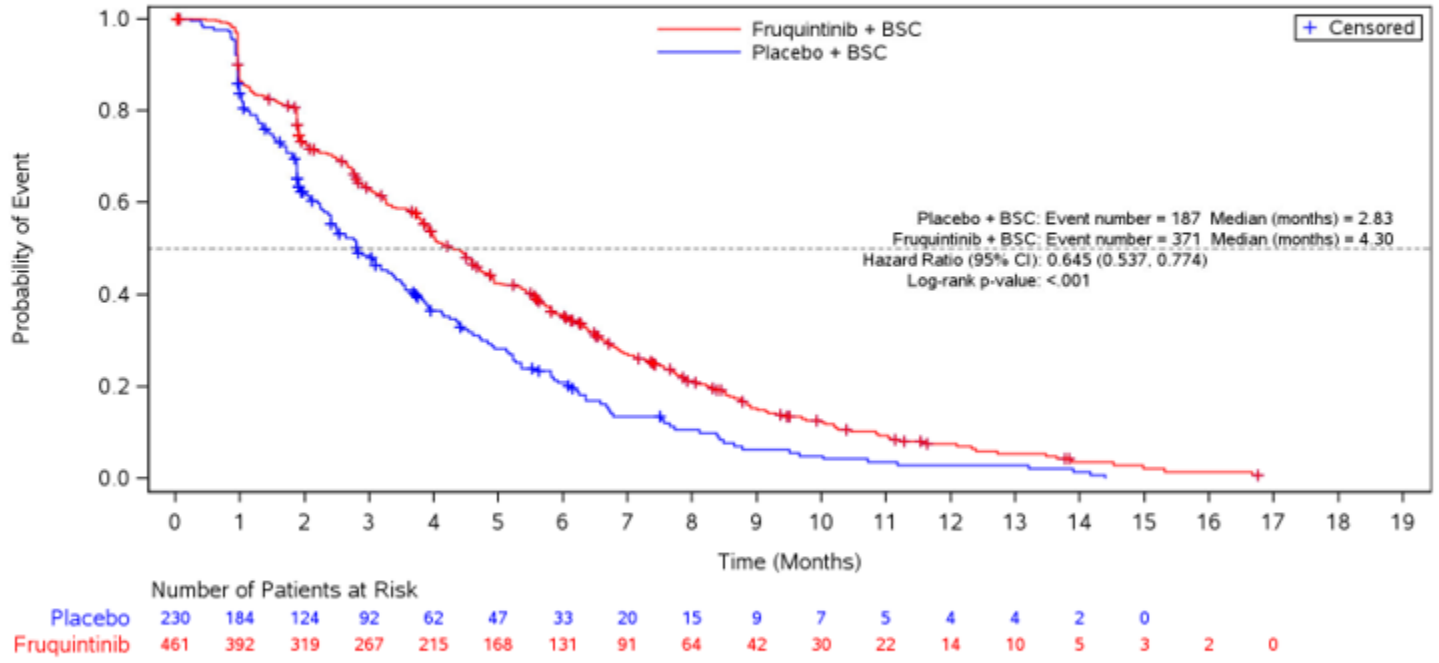


Number of Patients at Risk

Placebo	230	180	106	73	49	35	26	20	15	11	9	6	6	5	2	0				
Fruquintinib	461	365	276	212	163	117	89	59	38	26	17	12	6	2	2	2	1	1	1	0

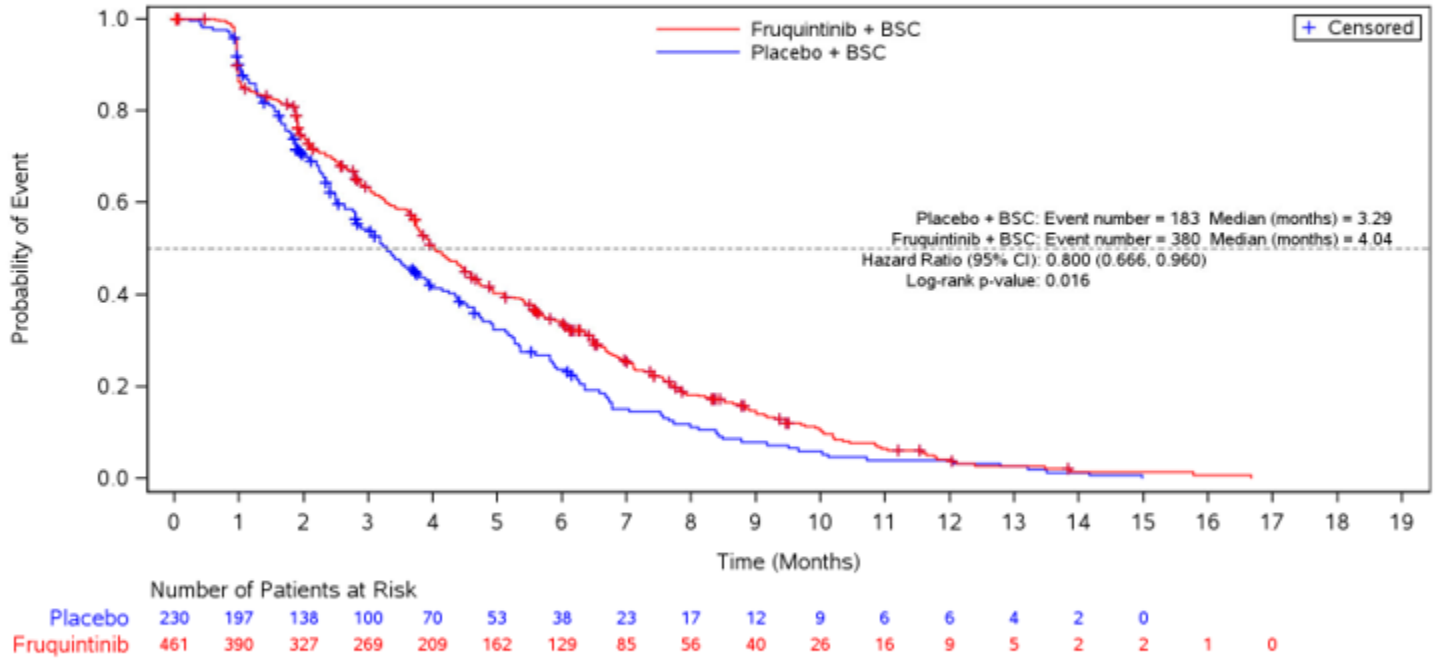
BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation



BSC=Best supportive care.

Figure 35.1.1.4.5A
Kaplan-Meier Plot for Time to Deterioration (Including Death) of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea



BSC=Best supportive care.

1.3.3 Responderanalyse – Zeit bis zur 1. Verschlechterung um ≥ 10 Punkte

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	107 (46.5)	247 (53.6)
Number of Subjects Censored, n (%)	123 (53.5)	214 (46.4)
Time to Deterioration (months)		
25% percentile (95% CI)	1.05 (0.99, 1.41)	1.45 (0.99, 1.87)
Median (95% CI)	2.76 (1.91, 5.52)	3.91 (2.86, 5.55)
75% percentile (95% CI)	NE (NE, NE)	NE (10.38, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.918 (0.117)
95% CI		(0.729, 1.156)
Log-rank p-value		0.467

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	48.3 (41.0, 55.6)	54.2 (49.5, 59.0)
6 months	41.3 (33.1, 49.4)	42.1 (36.9, 47.3)
9 months	41.3 (33.1, 49.4)	33.9 (28.0, 39.8)
12 months	41.3 (33.1, 49.4)	30.0 (22.7, 37.3)
18 months	NE (NE, NE)	30.0 (22.7, 37.3)
Median Follow-up Time (months)	1.87	2.43

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	90 (39.1)	257 (55.7)
Number of Subjects Censored, n (%)	140 (60.9)	204 (44.3)
Time to Deterioration (months)		
25% percentile (95% CI)	1.51 (0.99, 1.87)	1.28 (1.02, 1.87)
Median (95% CI)	NE (2.40, NE)	3.02 (2.76, 3.98)
75% percentile (95% CI)	NE (NE, NE)	15.44 (12.02, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.174 (0.124)
95% CI		(0.921, 1.496)
Log-rank p-value		0.195

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	55.2 (48.0, 62.5)	50.1 (45.3, 54.9)
6 months	51.3 (43.2, 59.3)	39.5 (34.5, 44.5)
9 months	51.3 (43.2, 59.3)	34.0 (28.4, 39.5)
12 months	51.3 (43.2, 59.3)	34.0 (28.4, 39.5)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	2.37

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	101 (43.9)	263 (57.0)
Number of Subjects Censored, n (%)	129 (56.1)	198 (43.0)
Time to Deterioration (months)		
25% percentile (95% CI)	1.15 (0.99, 1.68)	0.99 (0.99, 1.15)
Median (95% CI)	3.71 (2.10, NE)	2.83 (2.30, 3.81)
75% percentile (95% CI)	NE (NE, NE)	NE (8.44, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.095 (0.119)
95% CI		(0.868, 1.382)
Log-rank p-value		0.444

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	50.7 (43.3, 58.1)	48.0 (43.2, 52.8)
6 months	43.5 (35.1, 51.9)	38.8 (33.7, 43.8)
9 months	41.3 (32.3, 50.3)	30.1 (24.1, 36.1)
12 months	41.3 (32.3, 50.3)	30.1 (24.1, 36.1)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	2.04

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	71 (30.9)	185 (40.1)
Number of Subjects Censored, n (%)	159 (69.1)	276 (59.9)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.84, 2.17)	2.00 (1.91, 2.66)
Median (95% CI)	NE (NE, NE)	9.46 (6.47, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.030 (0.141)
95% CI		(0.781, 1.359)
Log-rank p-value		0.832

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	64.0 (57.0, 71.0)	66.8 (62.3, 71.3)
6 months	62.0 (54.7, 69.4)	56.7 (51.6, 61.9)
9 months	60.1 (52.1, 68.1)	50.1 (44.2, 55.9)
12 months	60.1 (52.1, 68.1)	45.9 (37.9, 53.8)
18 months	NE (NE, NE)	41.3 (30.1, 52.4)
Median Follow-up Time (months)	2.10	3.65

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	76 (33.0)	230 (49.9)
Number of Subjects Censored, n (%)	154 (67.0)	231 (50.1)
Time to Deterioration (months)		
25% percentile (95% CI)	1.84 (1.08, 1.91)	1.87 (1.77, 1.91)
Median (95% CI)	NE (5.59, NE)	3.98 (3.02, 5.98)
75% percentile (95% CI)	NE (NE, NE)	NE (12.02, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.281 (0.133)
95% CI		(0.987, 1.664)
Log-rank p-value		0.062

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	62.9 (55.9, 69.9)	54.9 (50.2, 59.7)
6 months	58.0 (49.9, 66.0)	44.8 (39.7, 50.0)
9 months	58.0 (49.9, 66.0)	38.5 (32.3, 44.6)
12 months	58.0 (49.9, 66.0)	38.5 (32.3, 44.6)
18 months	NE (NE, NE)	33.0 (21.7, 44.2)
Median Follow-up Time (months)	1.94	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	80 (34.8)	223 (48.4)
Number of Subjects Censored, n (%)	150 (65.2)	238 (51.6)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.38, 1.91)	1.87 (1.18, 1.91)
Median (95% CI)	NE (2.83, NE)	4.67 (3.71, 7.00)
75% percentile (95% CI)	NE (NE, NE)	NE (12.02, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.111 (0.132)
95% CI		(0.858, 1.439)
Log-rank p-value		0.424

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	56.7 (49.2, 64.1)	56.6 (51.8, 61.3)
6 months	56.7 (49.2, 64.1)	48.3 (43.2, 53.4)
9 months	56.7 (49.2, 64.1)	42.6 (36.8, 48.4)
12 months	56.7 (49.2, 64.1)	38.0 (30.9, 45.1)
18 months	NE (NE, NE)	34.2 (24.7, 43.8)
Median Follow-up Time (months)	1.91	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	128 (55.7)	292 (63.3)
Number of Subjects Censored, n (%)	102 (44.3)	169 (36.7)
Time to Deterioration (months)		
25% percentile (95% CI)	0.99 (0.95, 1.02)	0.99 (0.95, 0.99)
Median (95% CI)	1.87 (1.84, 2.10)	1.94 (1.87, 2.37)
75% percentile (95% CI)	NE (4.70, NE)	10.25 (7.00, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.7*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.933 (0.107)
95% CI		(0.756, 1.152)
Log-rank p-value		0.521

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	37.9 (30.8, 45.0)	39.5 (34.8, 44.2)
6 months	31.7 (24.2, 39.2)	32.6 (27.9, 37.4)
9 months	31.7 (24.2, 39.2)	26.6 (21.3, 31.9)
12 months	31.7 (24.2, 39.2)	22.6 (15.8, 29.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.56	1.87

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	65 (28.3)	169 (36.7)
Number of Subjects Censored, n (%)	165 (71.7)	292 (63.3)
Time to Deterioration (months)		
25% percentile (95% CI)	1.91 (1.87, 3.71)	2.56 (1.94, 3.06)
Median (95% CI)	NE (NE, NE)	18.63 (7.89, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.63, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.999 (0.148)
95% CI		(0.748, 1.334)
Log-rank p-value		0.993

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	70.5 (63.9, 77.1)	71.0 (66.7, 75.4)
6 months	61.3 (52.8, 69.8)	59.9 (54.9, 65.0)
9 months	61.3 (52.8, 69.8)	53.3 (47.3, 59.3)
12 months	61.3 (52.8, 69.8)	50.9 (43.5, 58.3)
18 months	NE (NE, NE)	50.9 (43.5, 58.3)
Median Follow-up Time (months)	2.18	3.75

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	94 (40.9)	276 (59.9)
Number of Subjects Censored, n (%)	136 (59.1)	185 (40.1)
Time to Deterioration (months)		
25% percentile (95% CI)	1.02 (0.99, 1.25)	0.99 (0.95, 0.99)
Median (95% CI)	NE (2.14, NE)	2.76 (1.94, 2.86)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.300 (0.120)
95% CI		(1.027, 1.645)
Log-rank p-value		0.029

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	53.5 (46.3, 60.8)	44.4 (39.6, 49.1)
6 months	50.3 (42.6, 58.1)	33.4 (28.4, 38.3)
9 months	50.3 (42.6, 58.1)	30.2 (25.0, 35.4)
12 months	50.3 (42.6, 58.1)	30.2 (25.0, 35.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.87	1.91

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	85 (37.0)	166 (36.0)
Number of Subjects Censored, n (%)	145 (63.0)	295 (64.0)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.02, 1.91)	1.91 (1.87, 2.92)
Median (95% CI)	NE (3.71, NE)	NE (9.07, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.7*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.717 (0.136)
95% CI		(0.550, 0.936)
Log-rank p-value		0.014

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	58.9 (51.7, 66.1)	70.2 (65.8, 74.5)
6 months	50.8 (41.9, 59.6)	60.4 (55.3, 65.4)
9 months	50.8 (41.9, 59.6)	56.7 (51.0, 62.4)
12 months	50.8 (41.9, 59.6)	50.1 (41.0, 59.3)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.91	3.71

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	81 (35.2)	189 (41.0)
Number of Subjects Censored, n (%)	149 (64.8)	272 (59.0)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.15, 1.91)	1.97 (1.87, 2.63)
Median (95% CI)	NE (4.67, NE)	7.89 (6.47, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.827 (0.135)
95% CI		(0.634, 1.078)
Log-rank p-value		0.159

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	59.1 (52.0, 66.3)	65.0 (60.4, 69.6)
6 months	55.1 (47.0, 63.1)	56.4 (51.4, 61.4)
9 months	55.1 (47.0, 63.1)	49.0 (43.2, 54.9)
12 months	55.1 (47.0, 63.1)	47.1 (40.4, 53.9)
18 months	NE (NE, NE)	47.1 (40.4, 53.9)
Median Follow-up Time (months)	1.91	3.25

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	76 (33.0)	233 (50.5)
Number of Subjects Censored, n (%)	154 (67.0)	228 (49.5)
Time to Deterioration (months)		
25% percentile (95% CI)	1.87 (1.31, 1.94)	1.87 (1.18, 1.91)
Median (95% CI)	NE (5.59, NE)	4.57 (3.75, 5.85)
75% percentile (95% CI)	NE (NE, NE)	15.44 (10.38, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.221 (0.134)
95% CI		(0.939, 1.589)
Log-rank p-value		0.136

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	62.2 (55.0, 69.4)	58.2 (53.5, 63.0)
6 months	57.1 (48.7, 65.4)	44.8 (39.6, 50.1)
9 months	54.9 (45.8, 63.9)	36.5 (30.1, 42.9)
12 months	54.9 (45.8, 63.9)	30.8 (22.8, 38.9)
18 months	NE (NE, NE)	15.4 (0.0, 37.1)
Median Follow-up Time (months)	1.91	2.79

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	56 (24.3)	158 (34.3)
Number of Subjects Censored, n (%)	174 (75.7)	303 (65.7)
Time to Deterioration (months)		
25% percentile (95% CI)	2.10 (1.87, NE)	2.76 (1.91, 3.22)
Median (95% CI)	NE (NE, NE)	NE (8.90, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.122 (0.157)
95% CI		(0.825, 1.526)
Log-rank p-value		0.461

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	72.6 (66.2, 79.0)	71.7 (67.4, 76.0)
6 months	69.5 (62.4, 76.5)	62.3 (57.3, 67.3)
9 months	69.5 (62.4, 76.5)	55.2 (48.7, 61.8)
12 months	69.5 (62.4, 76.5)	53.2 (45.7, 60.6)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.28	3.84

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	30 (13.0)	155 (33.6)
Number of Subjects Censored, n (%)	200 (87.0)	306 (66.4)
Time to Deterioration (months)		
25% percentile (95% CI)	NE (NE, NE)	2.79 (1.97, 3.68)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.7*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.225 (0.200)
95% CI		(1.503, 3.294)
Log-rank p-value		<.001

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	86.1 (81.1, 91.0)	73.1 (68.9, 77.3)
6 months	82.4 (76.2, 88.7)	62.2 (57.1, 67.2)
9 months	82.4 (76.2, 88.7)	57.4 (51.5, 63.3)
12 months	82.4 (76.2, 88.7)	57.4 (51.5, 63.3)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.51	3.75

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	46 (20.0)	107 (23.2)
Number of Subjects Censored, n (%)	184 (80.0)	354 (76.8)
Time to Deterioration (months)		
25% percentile (95% CI)	4.04 (2.07, NE)	7.39 (3.19, 9.92)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.893 (0.178)
95% CI		(0.630, 1.267)
Log-rank p-value		0.525

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.3A
Summary of Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	75.2 (68.7, 81.7)	79.7 (75.8, 83.5)
6 months	74.1 (67.3, 80.9)	76.1 (71.8, 80.3)
9 months	74.1 (67.3, 80.9)	71.5 (66.0, 76.9)
12 months	74.1 (67.3, 80.9)	64.6 (56.5, 72.8)
18 months	NE (NE, NE)	64.6 (56.5, 72.8)
Median Follow-up Time (months)	2.35	4.30

* indicates censored value.

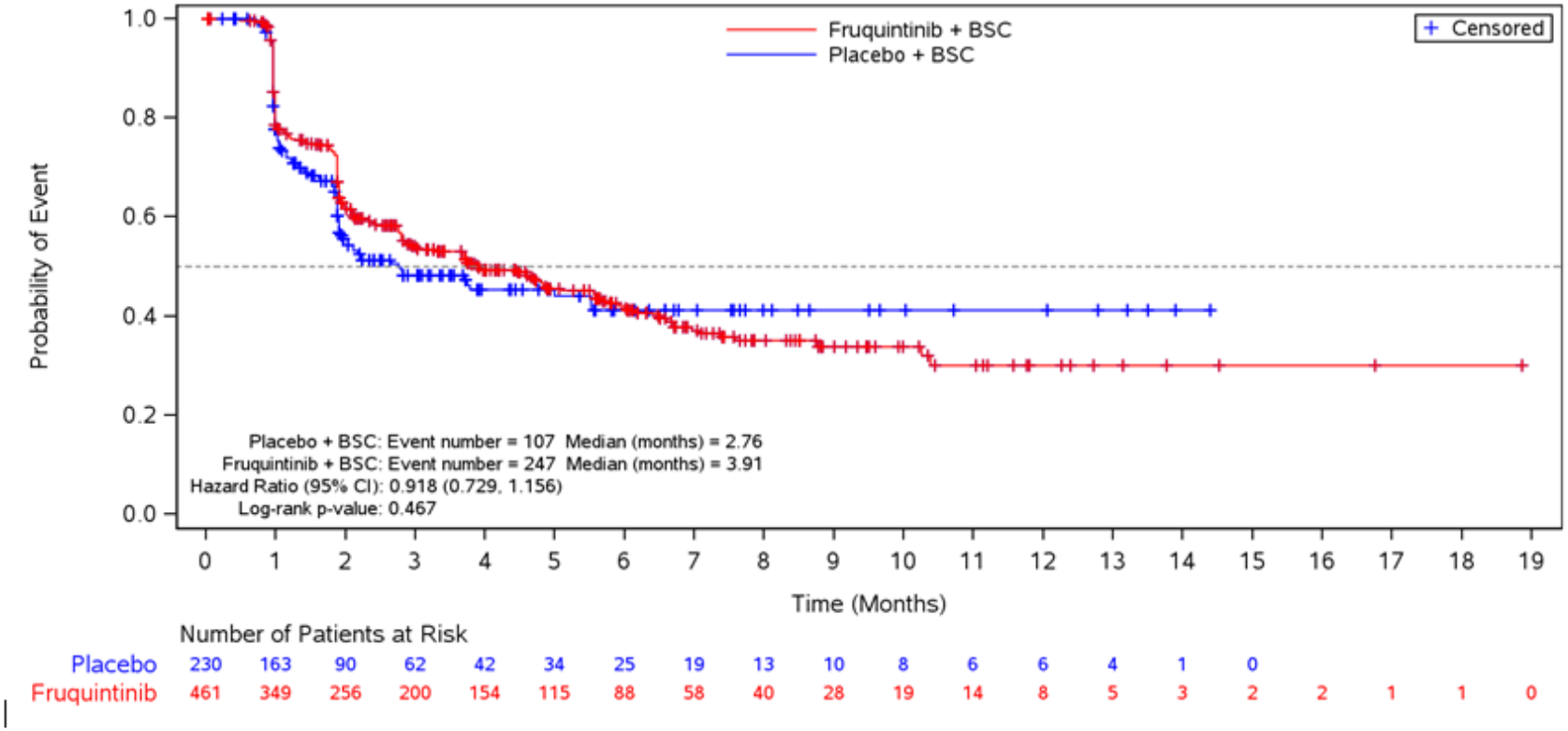
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

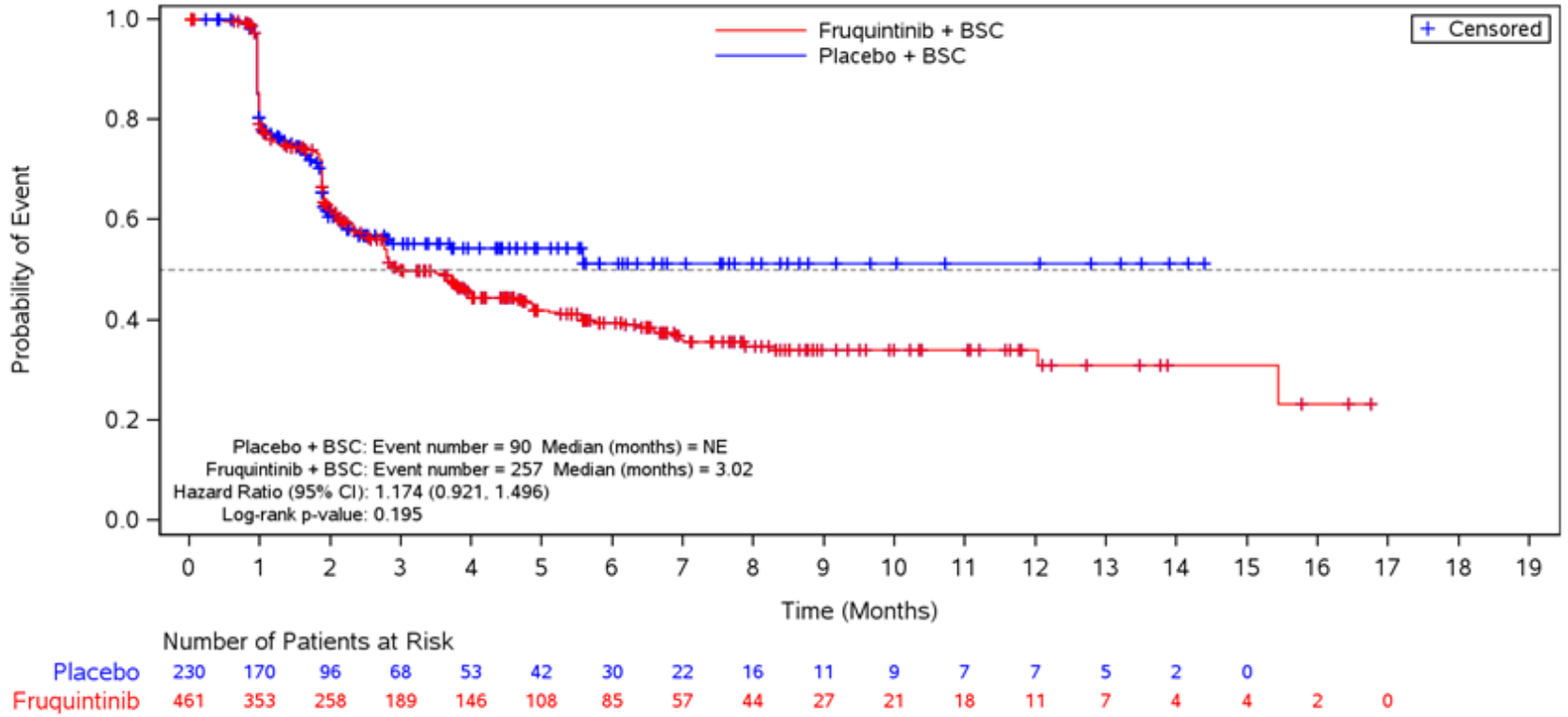
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL



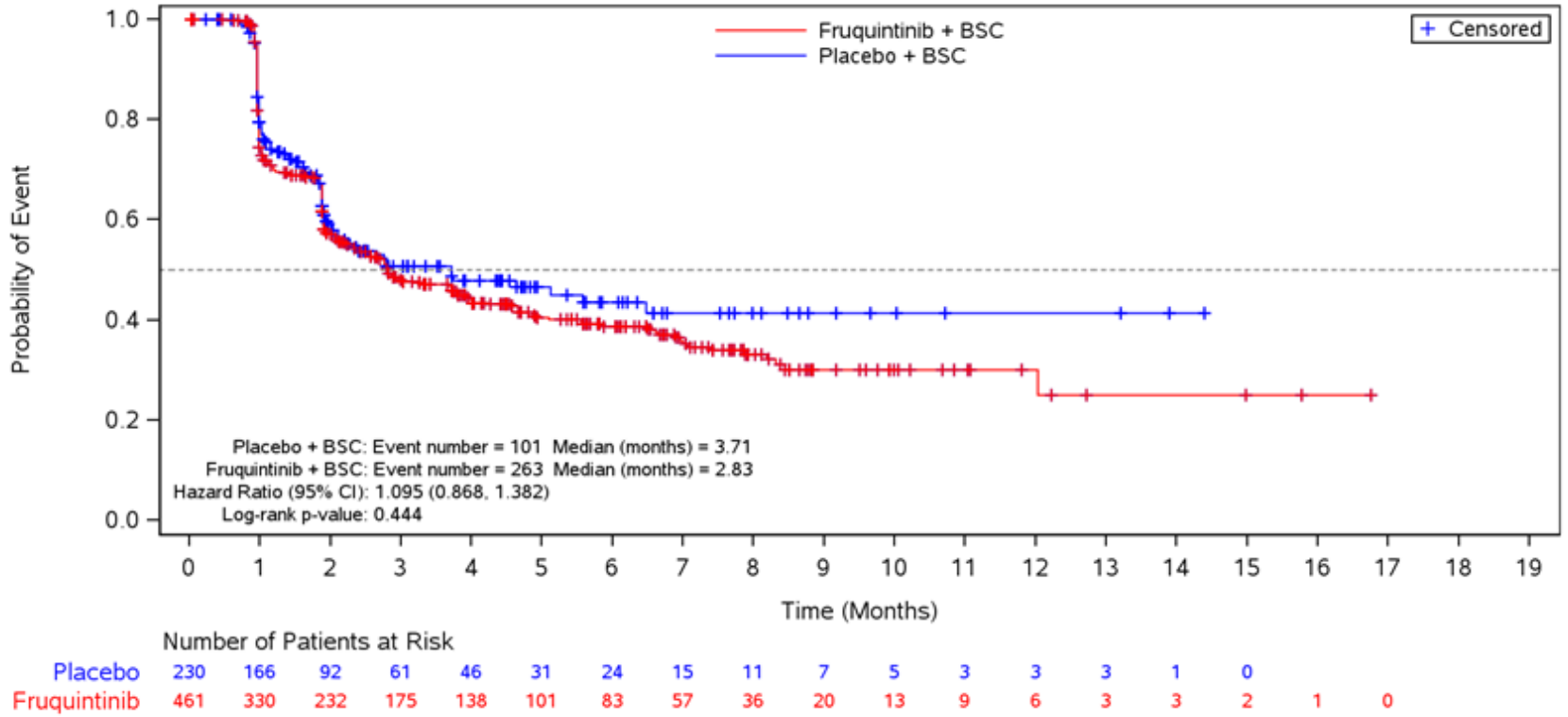
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning



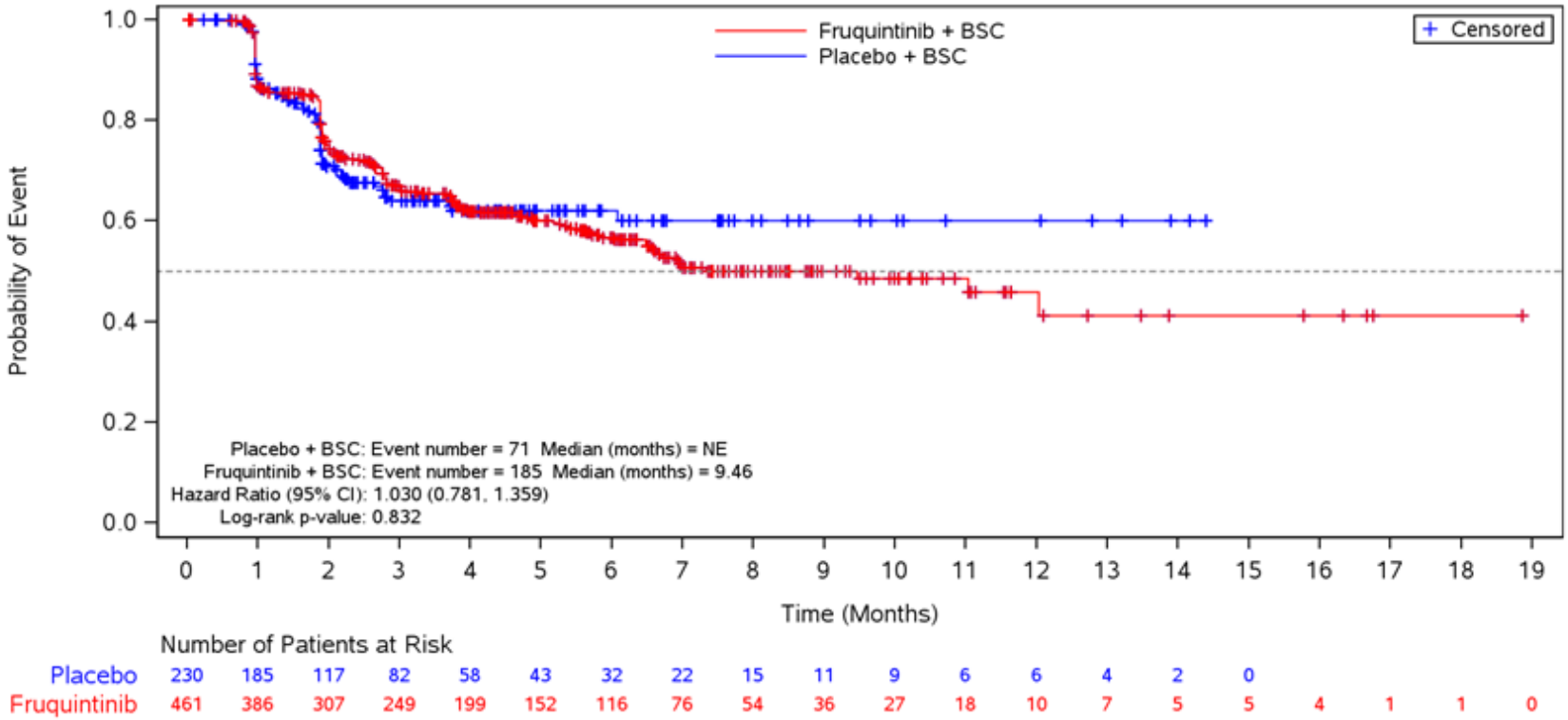
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning



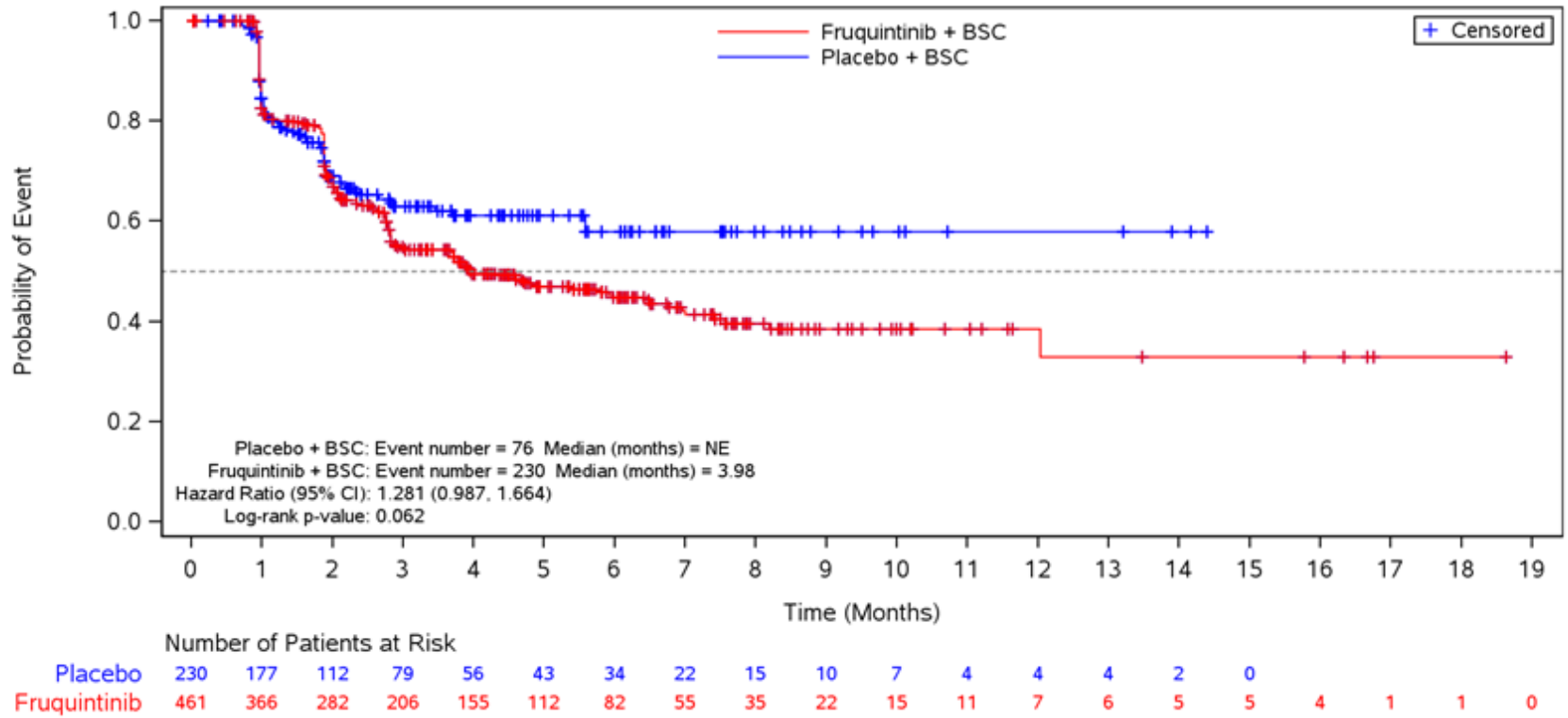
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning



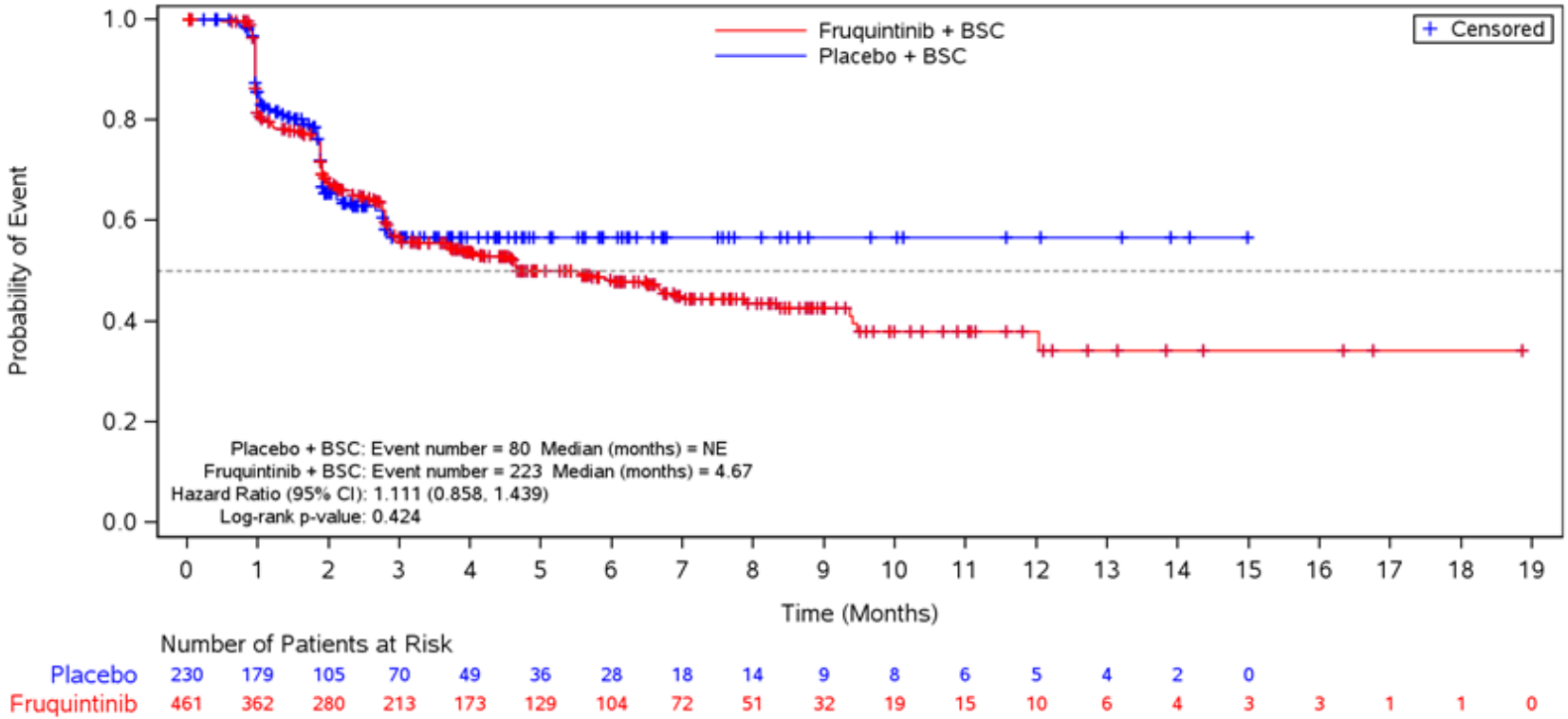
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning



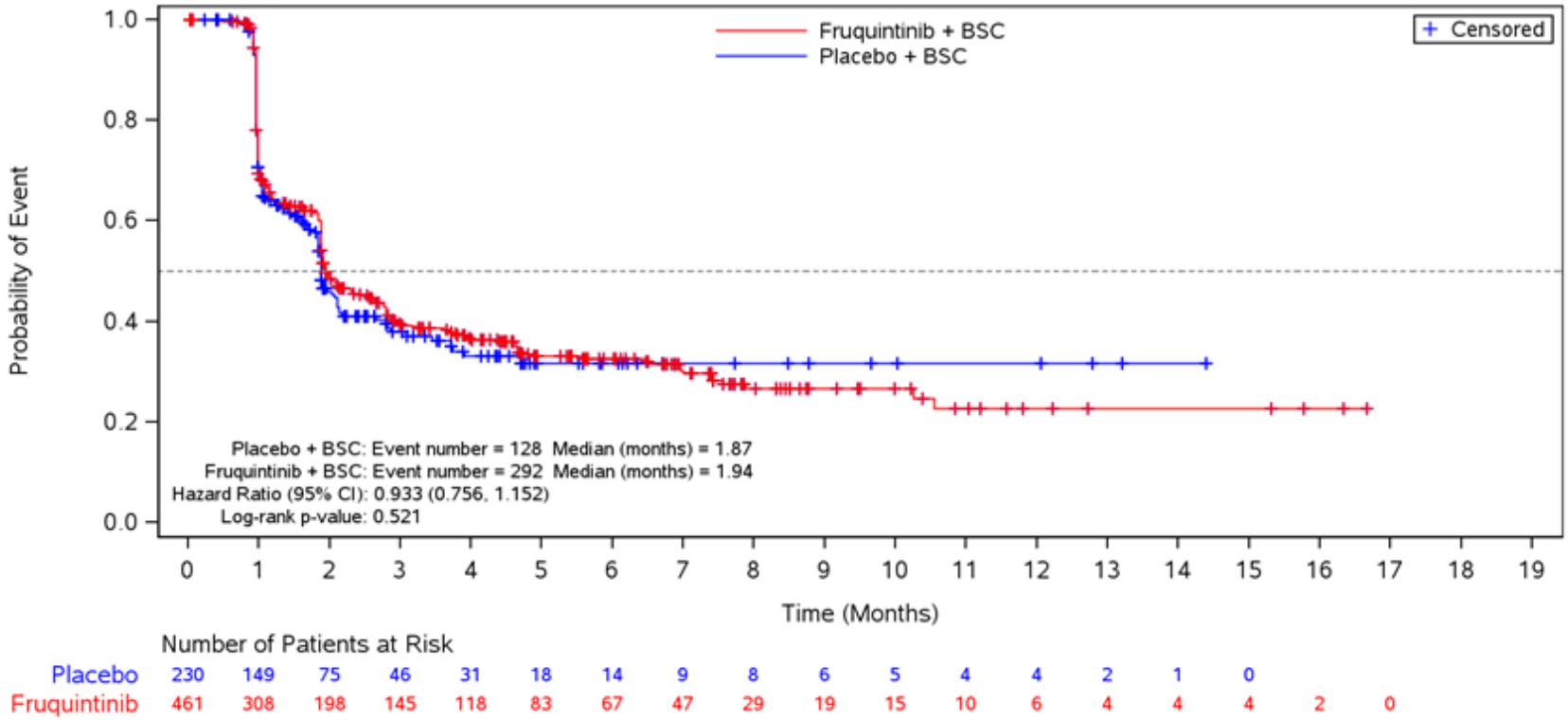
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning



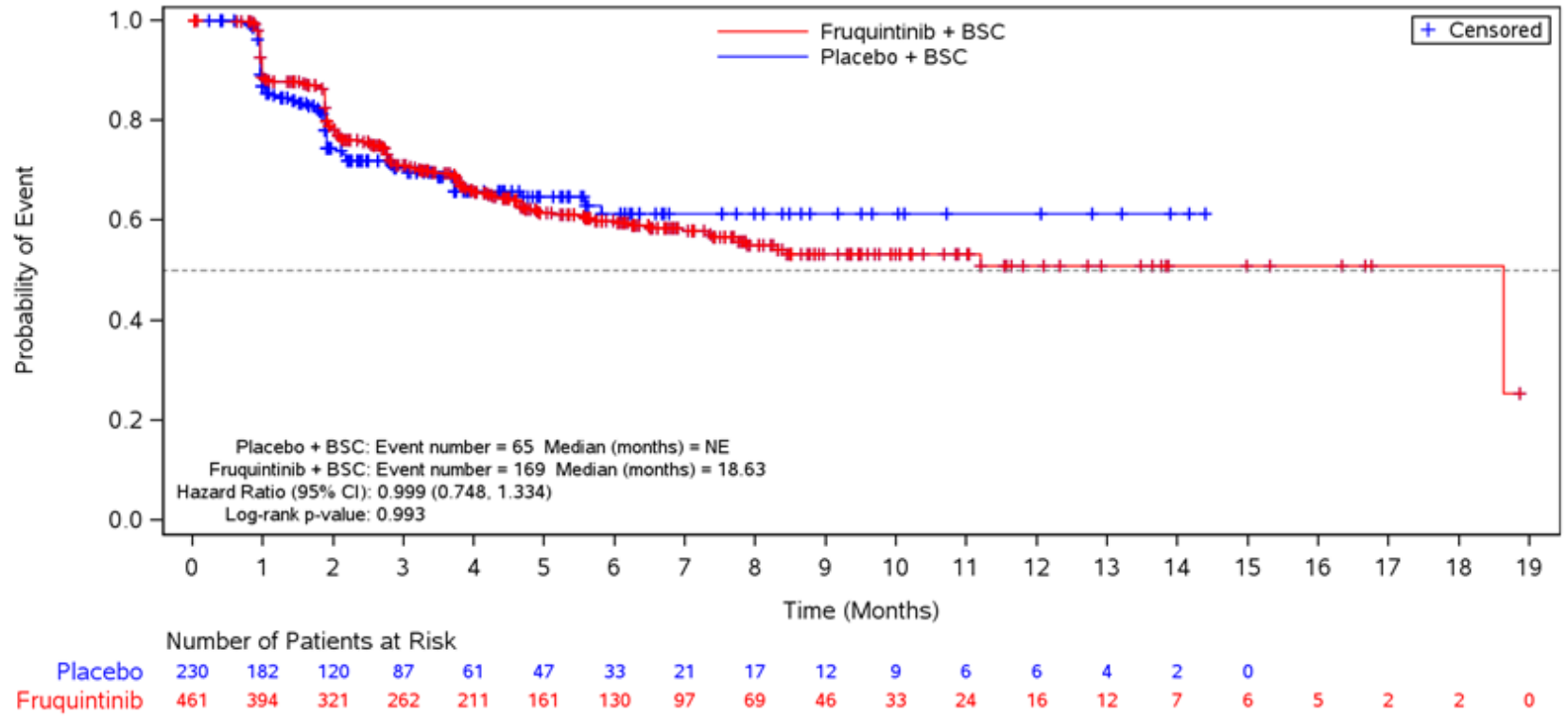
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue



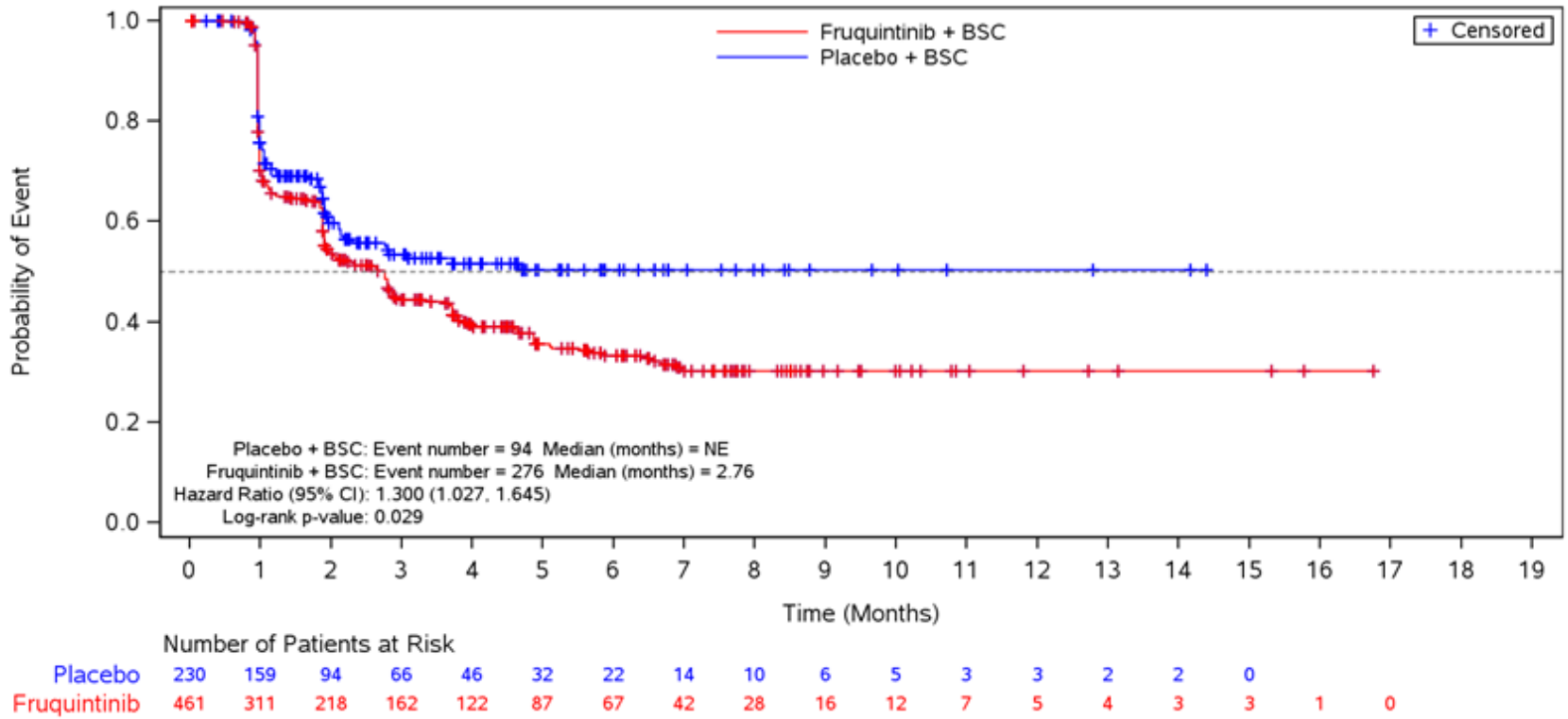
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting



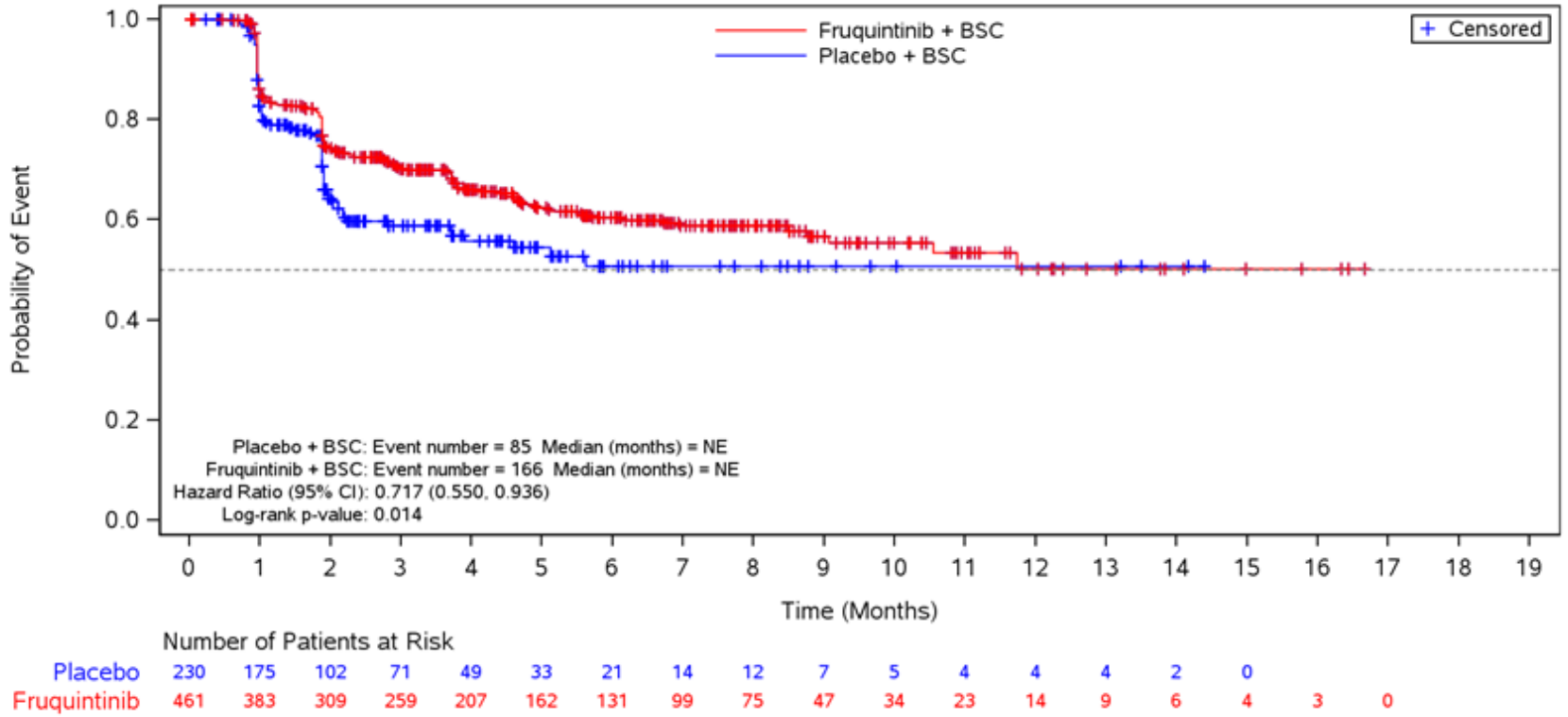
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain



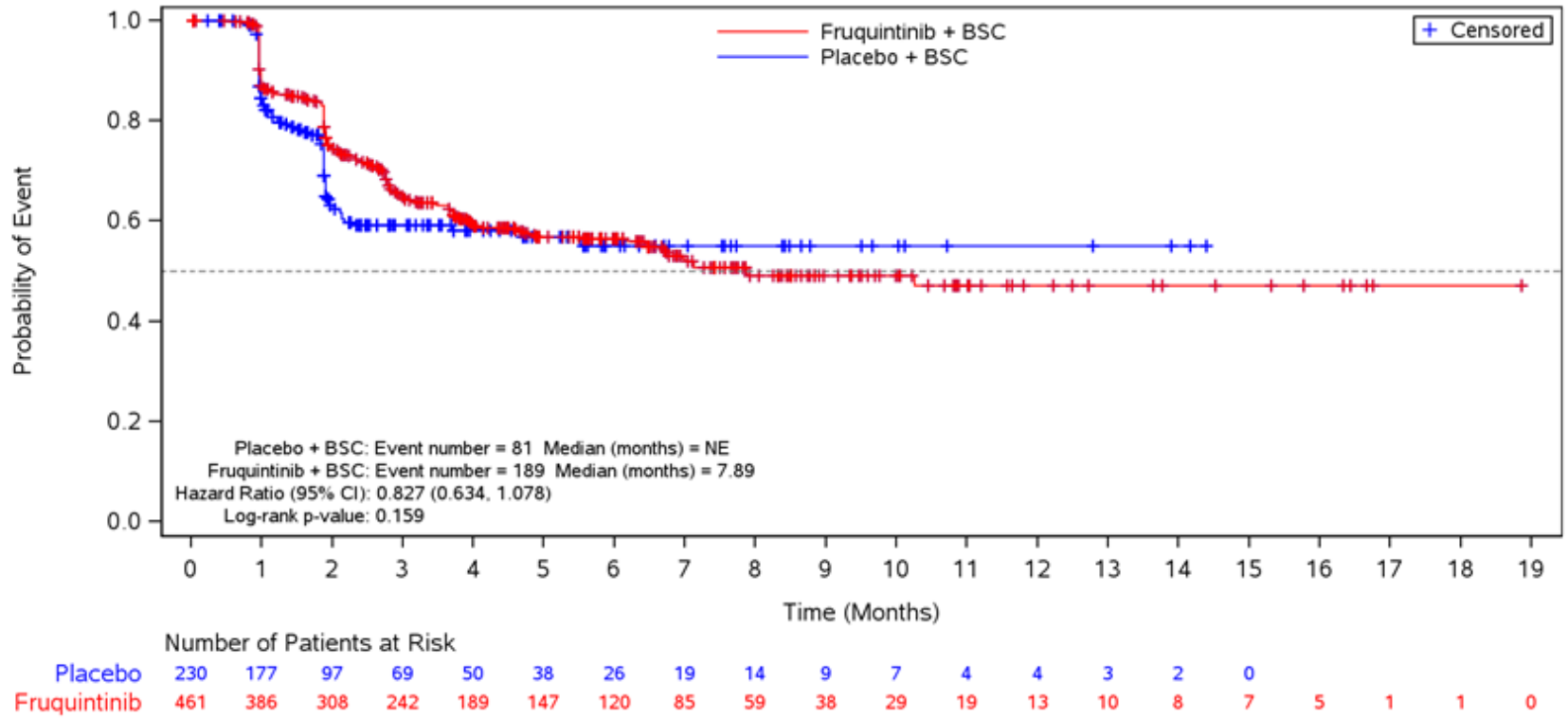
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea



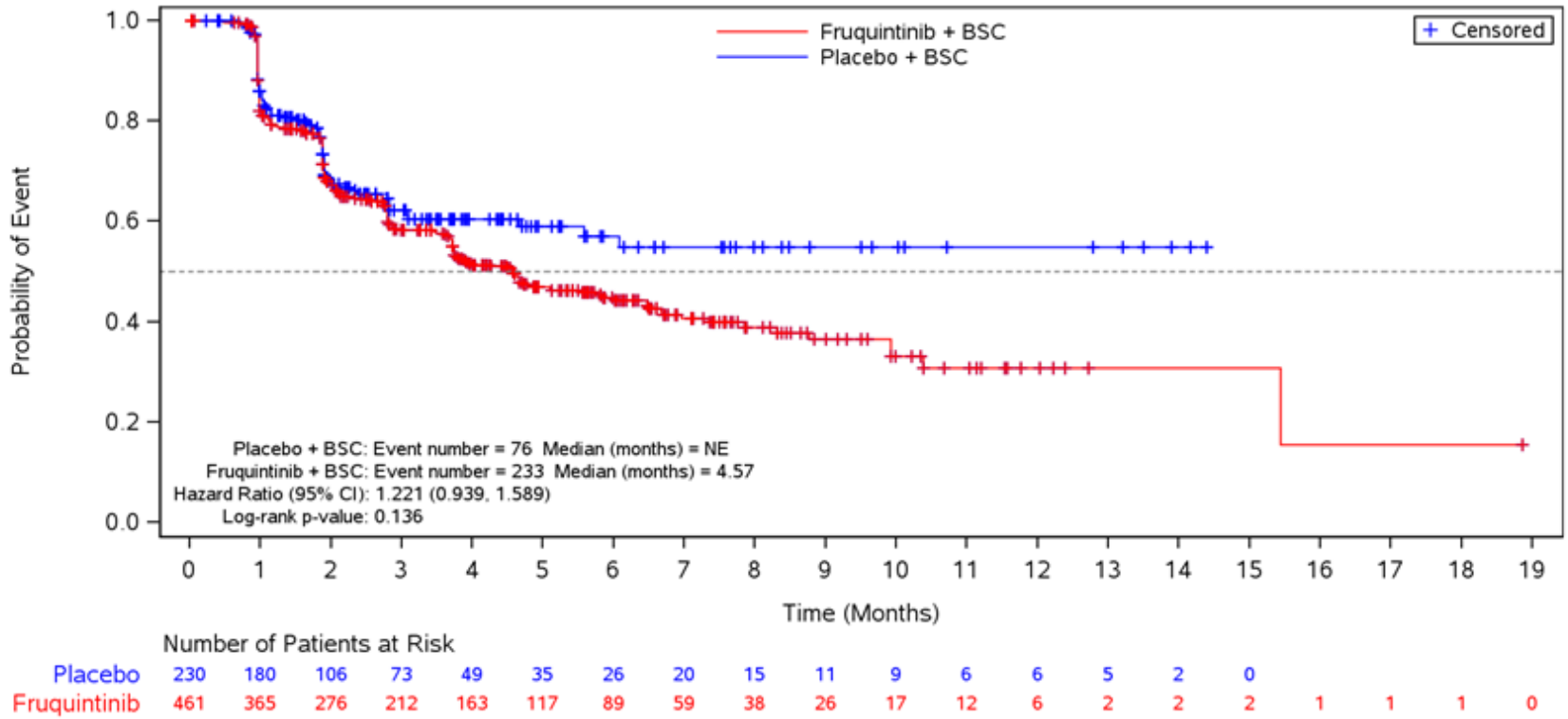
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia



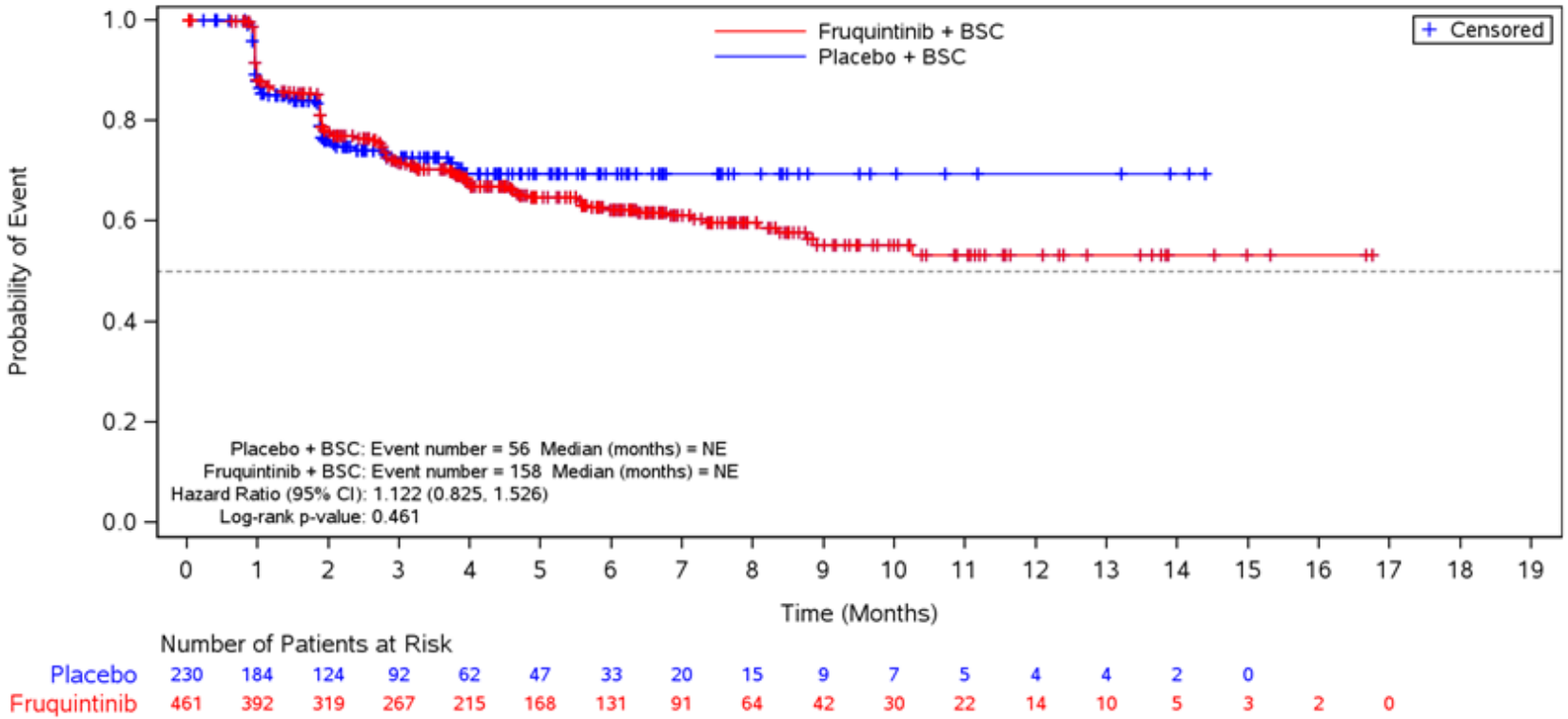
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss



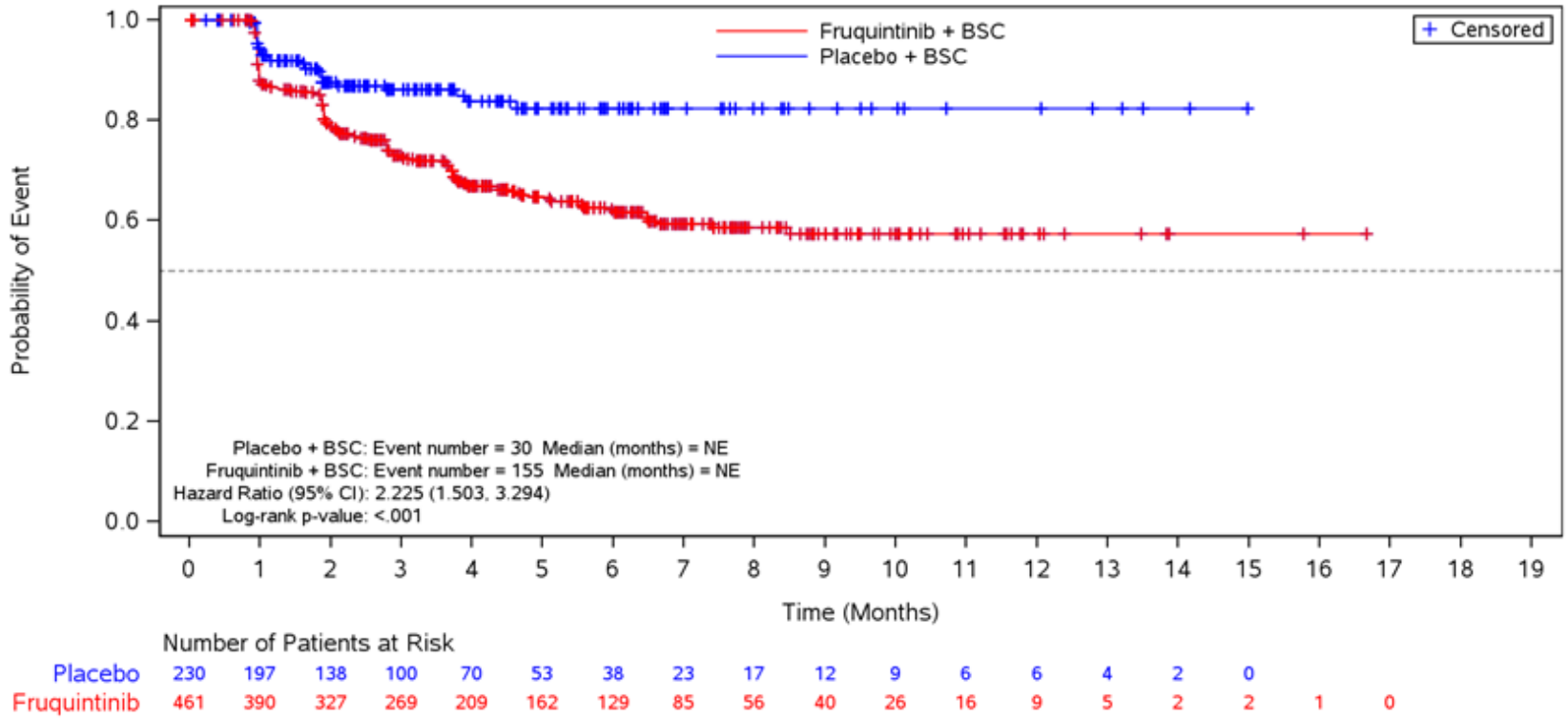
BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation



BSC=Best supportive care.

Figure 35.1.1.4.3A
Kaplan-Meier Plot for Time to Deterioration of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea



BSC=Best supportive care.

1.3.4 Responderanalyse − Zeit bis zur 1. Verbesserung um ≥ 10 Punkte

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	37 (16.1)	121 (26.2)
Number of Subjects Censored, n (%)	193 (83.9)	340 (73.8)
Time to Improvement (months)		
25% percentile (95% CI)	NE (3.68, NE)	3.71 (2.10, 6.67)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.419 (0.189)
95% CI		(0.981, 2.054)
Log-rank p-value		0.062

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	82.4 (77.0, 87.8)	76.6 (72.6, 80.6)
6 months	80.5 (74.7, 86.4)	71.6 (67.2, 76.1)
9 months	80.5 (74.7, 86.4)	69.4 (64.4, 74.4)
12 months	80.5 (74.7, 86.4)	69.4 (64.4, 74.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.43	3.88

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	32 (13.9)	85 (18.4)
Number of Subjects Censored, n (%)	198 (86.1)	376 (81.6)
Time to Improvement (months)		
25% percentile (95% CI)	NE (4.63, NE)	NE (6.01, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.154 (0.208)
95% CI		(0.767, 1.736)
Log-rank p-value		0.492

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	85.0 (79.9, 90.1)	82.8 (79.2, 86.4)
6 months	81.4 (75.0, 87.7)	79.6 (75.6, 83.5)
9 months	81.4 (75.0, 87.7)	79.1 (75.0, 83.1)
12 months	81.4 (75.0, 87.7)	79.1 (75.0, 83.1)
18 months	NE (NE, NE)	79.1 (75.0, 83.1)
Median Follow-up Time (months)	2.58	4.21

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	43 (18.7)	116 (25.2)
Number of Subjects Censored, n (%)	187 (81.3)	345 (74.8)
Time to Improvement (months)		
25% percentile (95% CI)	NE (2.23, NE)	3.81 (2.73, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.167 (0.179)
95% CI		(0.822, 1.658)
Log-rank p-value		0.388

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	79.7 (74.1, 85.3)	76.4 (72.3, 80.4)
6 months	77.6 (71.4, 83.8)	71.5 (67.0, 76.1)
9 months	77.6 (71.4, 83.8)	71.0 (66.4, 75.7)
12 months	77.6 (71.4, 83.8)	71.0 (66.4, 75.7)
18 months	NE (NE, NE)	71.0 (66.4, 75.7)
Median Follow-up Time (months)	2.40	3.94

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	41 (17.8)	131 (28.4)
Number of Subjects Censored, n (%)	189 (82.2)	330 (71.6)
Time to Improvement (months)		
25% percentile (95% CI)	NE (2.76, NE)	2.76 (1.91, 3.88)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.4*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.451 (0.180)
95% CI		(1.021, 2.063)
Log-rank p-value		0.037

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	79.5 (73.6, 85.4)	72.5 (68.2, 76.7)
6 months	76.4 (69.3, 83.5)	68.1 (63.4, 72.8)
9 months	76.4 (69.3, 83.5)	67.4 (62.5, 72.2)
12 months	76.4 (69.3, 83.5)	67.4 (62.5, 72.2)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.40	3.71

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	46 (20.0)	98 (21.3)
Number of Subjects Censored, n (%)	184 (80.0)	363 (78.7)
Time to Improvement (months)		
25% percentile (95% CI)	NE (1.91, NE)	10.64 (3.71, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.907 (0.180)
95% CI		(0.637, 1.290)
Log-rank p-value		0.586

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	78.2 (72.4, 83.9)	81.7 (78.0, 85.4)
6 months	76.5 (70.5, 82.6)	76.3 (72.1, 80.6)
9 months	76.5 (70.5, 82.6)	75.7 (71.3, 80.1)
12 months	76.5 (70.5, 82.6)	73.6 (67.7, 79.5)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.30	3.98

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	59 (25.7)	141 (30.6)
Number of Subjects Censored, n (%)	171 (74.3)	320 (69.4)
Time to Improvement (months)		
25% percentile (95% CI)	1.71 (0.99, NE)	1.87 (1.15, 2.79)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.049 (0.156)
95% CI		(0.772, 1.424)
Log-rank p-value		0.759

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	71.8 (65.5, 78.0)	69.7 (65.4, 74.1)
6 months	70.8 (64.3, 77.2)	66.9 (62.2, 71.5)
9 months	70.8 (64.3, 77.2)	65.6 (60.4, 70.8)
12 months	70.8 (64.3, 77.2)	63.4 (56.9, 69.9)
18 months	NE (NE, NE)	63.4 (56.9, 69.9)
Median Follow-up Time (months)	2.04	3.38

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	57 (24.8)	162 (35.1)
Number of Subjects Censored, n (%)	173 (75.2)	299 (64.9)
Time to Improvement (months)		
25% percentile (95% CI)	1.91 (1.22, NE)	1.87 (1.18, 2.79)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.4*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.251 (0.155)
95% CI		(0.923, 1.693)
Log-rank p-value		0.148

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	72.2 (65.9, 78.6)	68.0 (63.6, 72.5)
6 months	70.2 (63.4, 77.0)	59.6 (54.5, 64.8)
9 months	70.2 (63.4, 77.0)	57.8 (52.2, 63.4)
12 months	70.2 (63.4, 77.0)	57.8 (52.2, 63.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.09	3.38

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	31 (13.5)	78 (16.9)
Number of Subjects Censored, n (%)	199 (86.5)	383 (83.1)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.144 (0.213)
95% CI		(0.754, 1.736)
Log-rank p-value		0.527

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	85.1 (80.1, 90.1)	82.8 (79.3, 86.4)
6 months	83.8 (78.3, 89.3)	82.2 (78.6, 85.8)
9 months	83.8 (78.3, 89.3)	81.7 (78.0, 85.5)
12 months	83.8 (78.3, 89.3)	81.7 (78.0, 85.5)
18 months	NE (NE, NE)	81.7 (78.0, 85.5)
Median Follow-up Time (months)	2.58	4.50

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	52 (22.6)	145 (31.5)
Number of Subjects Censored, n (%)	178 (77.4)	316 (68.5)
Time to Improvement (months)		
25% percentile (95% CI)	2.83 (1.71, NE)	1.94 (1.87, 2.92)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.222 (0.162)
95% CI		(0.889, 1.679)
Log-rank p-value		0.216

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	73.5 (67.1, 79.8)	70.5 (66.1, 74.8)
6 months	73.5 (67.1, 79.8)	65.7 (61.0, 70.5)
9 months	73.5 (67.1, 79.8)	64.0 (58.9, 69.0)
12 months	73.5 (67.1, 79.8)	60.8 (53.0, 68.5)
18 months	NE (NE, NE)	60.8 (53.0, 68.5)
Median Follow-up Time (months)	2.28	3.68

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	29 (12.6)	90 (19.5)
Number of Subjects Censored, n (%)	201 (87.4)	371 (80.5)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (4.60, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.372 (0.214)
95% CI		(0.902, 2.088)
Log-rank p-value		0.138

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	85.7 (80.8, 90.5)	82.0 (78.4, 85.7)
6 months	85.7 (80.8, 90.5)	79.0 (75.1, 83.0)
9 months	85.7 (80.8, 90.5)	77.6 (73.3, 81.9)
12 months	85.7 (80.8, 90.5)	77.6 (73.3, 81.9)
18 months	NE (NE, NE)	77.6 (73.3, 81.9)
Median Follow-up Time (months)	2.48	4.27

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	39 (17.0)	123 (26.7)
Number of Subjects Censored, n (%)	191 (83.0)	338 (73.3)
Time to Improvement (months)		
25% percentile (95% CI)	NE (3.02, NE)	2.83 (1.87, 7.56)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 16.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.442 (0.185)
95% CI		(1.005, 2.071)
Log-rank p-value		0.046

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	81.5 (76.0, 87.0)	74.5 (70.4, 78.6)
6 months	78.7 (72.5, 84.9)	71.7 (67.3, 76.1)
9 months	78.7 (72.5, 84.9)	68.9 (63.6, 74.2)
12 months	78.7 (72.5, 84.9)	68.9 (63.6, 74.2)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.40	3.78

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	36 (15.7)	86 (18.7)
Number of Subjects Censored, n (%)	194 (84.3)	375 (81.3)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (6.90, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.068 (0.199)
95% CI		(0.723, 1.579)
Log-rank p-value		0.741

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	81.9 (76.5, 87.3)	82.4 (78.8, 86.0)
6 months	81.9 (76.5, 87.3)	79.7 (75.7, 83.6)
9 months	81.9 (76.5, 87.3)	79.0 (74.9, 83.1)
12 months	81.9 (76.5, 87.3)	79.0 (74.9, 83.1)
18 months	NE (NE, NE)	79.0 (74.9, 83.1)
Median Follow-up Time (months)	2.40	4.40

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	37 (16.1)	106 (23.0)
Number of Subjects Censored, n (%)	193 (83.9)	355 (77.0)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	6.54 (2.76, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.278 (0.192)
95% CI		(0.877, 1.860)
Log-rank p-value		0.200

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	81.6 (76.1, 87.0)	77.5 (73.6, 81.5)
6 months	81.6 (76.1, 87.0)	75.2 (70.9, 79.4)
9 months	81.6 (76.1, 87.0)	73.8 (69.2, 78.4)
12 months	81.6 (76.1, 87.0)	73.8 (69.2, 78.4)
18 months	NE (NE, NE)	73.8 (69.2, 78.4)
Median Follow-up Time (months)	2.40	3.94

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	33 (14.3)	74 (16.1)
Number of Subjects Censored, n (%)	197 (85.7)	387 (83.9)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 15.0*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.962 (0.210)
95% CI		(0.637, 1.452)
Log-rank p-value		0.854

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	84.2 (79.0, 89.3)	84.2 (80.8, 87.7)
6 months	82.3 (76.1, 88.5)	82.8 (79.1, 86.5)
9 months	82.3 (76.1, 88.5)	81.2 (77.0, 85.4)
12 months	82.3 (76.1, 88.5)	81.2 (77.0, 85.4)
18 months	NE (NE, NE)	81.2 (77.0, 85.4)
Median Follow-up Time (months)	2.48	4.57

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Number of Subjects with Events, n (%)	20 (8.7)	83 (18.0)
Number of Subjects Censored, n (%)	210 (91.3)	378 (82.0)
Time to Improvement (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 14.4*	0.0*, 18.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.881 (0.249)
95% CI		(1.154, 3.067)
Log-rank p-value		0.010

* indicates censored value.

Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.4.4A
Summary of Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Financial Difficulty

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=461
Kaplan-Meier Estimates at (95% CI)		
3 months	90.1 (86.0, 94.3)	83.2 (79.6, 86.7)
6 months	90.1 (86.0, 94.3)	79.5 (75.4, 83.5)
9 months	90.1 (86.0, 94.3)	79.5 (75.4, 83.5)
12 months	90.1 (86.0, 94.3)	79.5 (75.4, 83.5)
18 months	NE (NE, NE)	79.5 (75.4, 83.5)
Median Follow-up Time (months)	2.83	4.44

* indicates censored value.

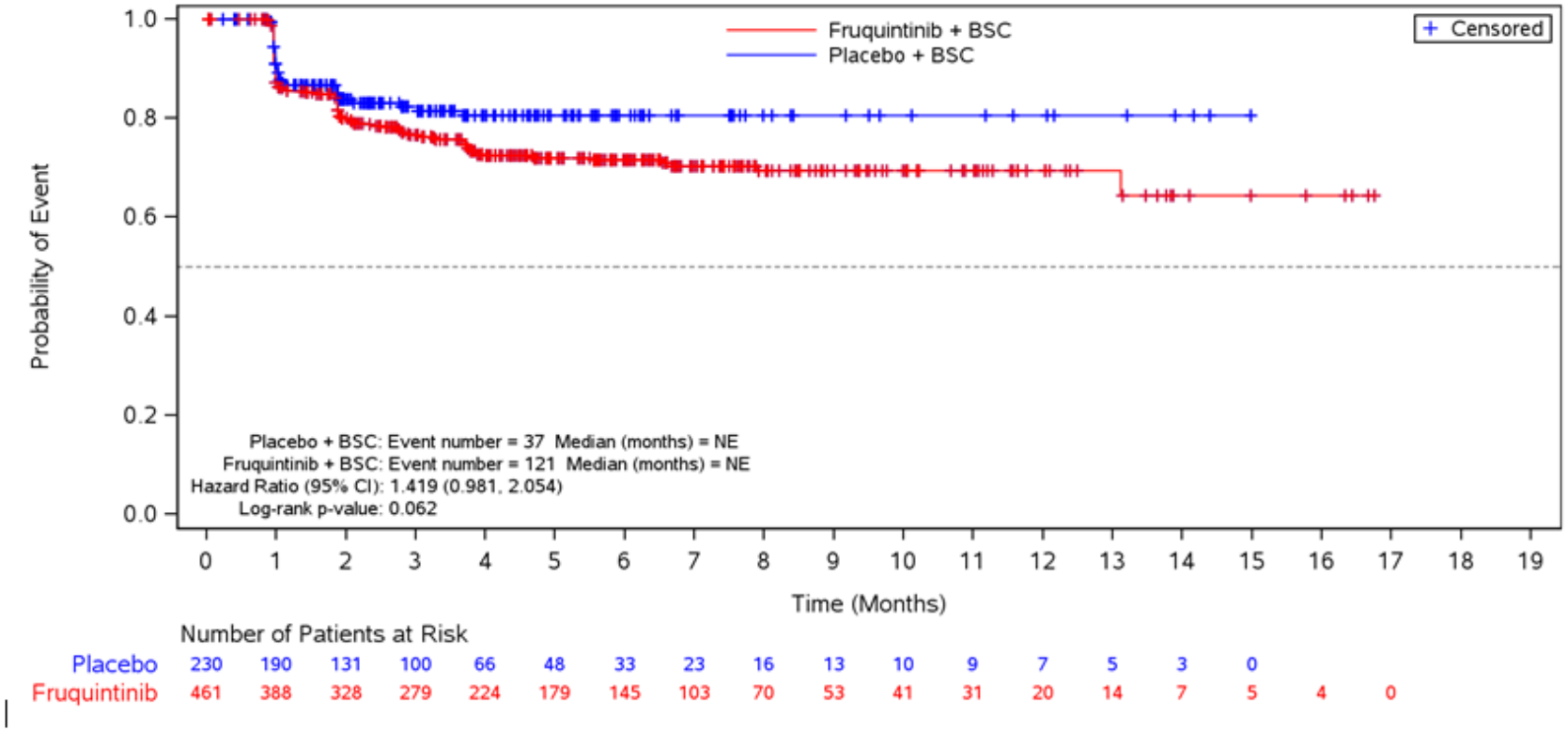
Note: The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model. Patients without event but with death record are censored at date of death, patients without event and death record are censored at the last date of observed measurement.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as (date of event/death/last date of observed measurement – randomization date + 1)/30.4375.

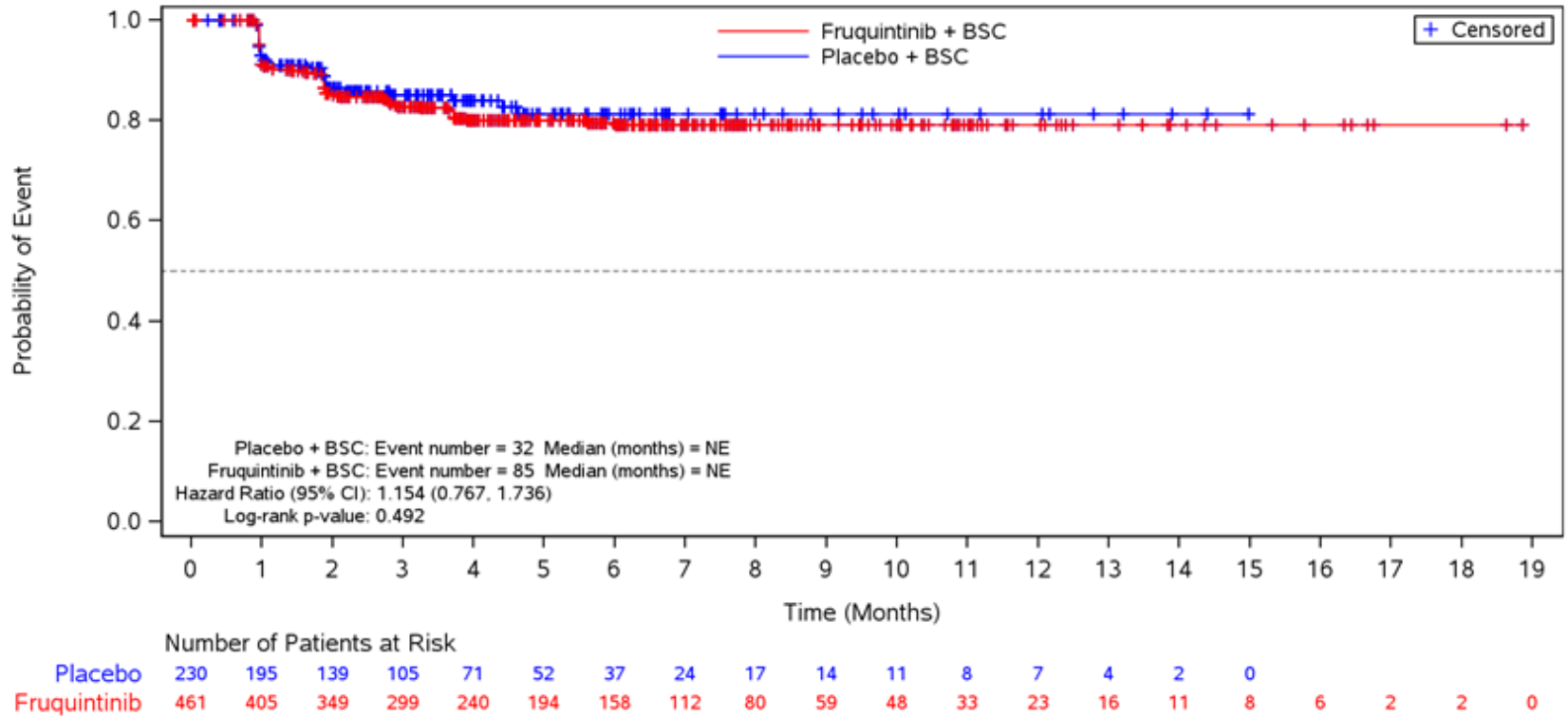
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Global health status/QoL



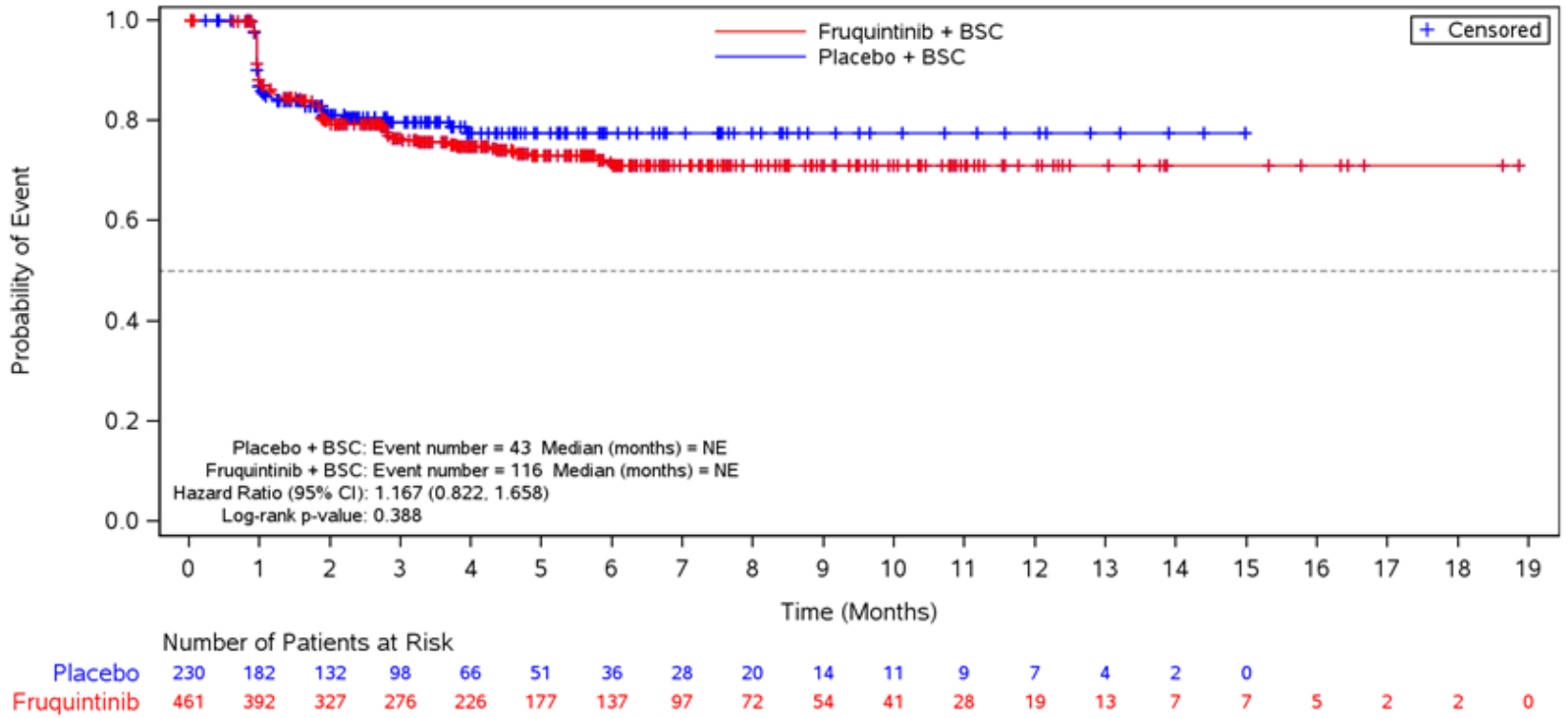
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Physical Functioning



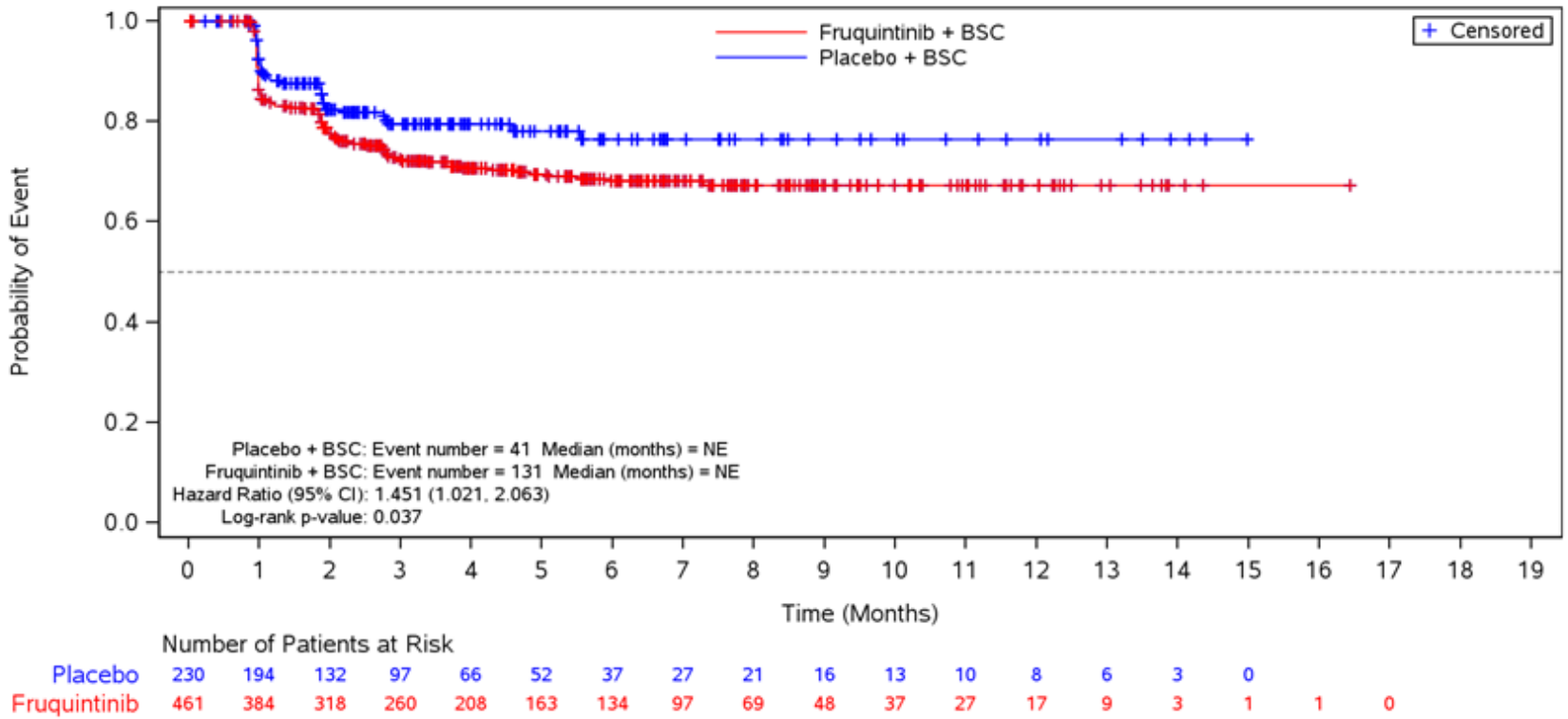
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Role Functioning



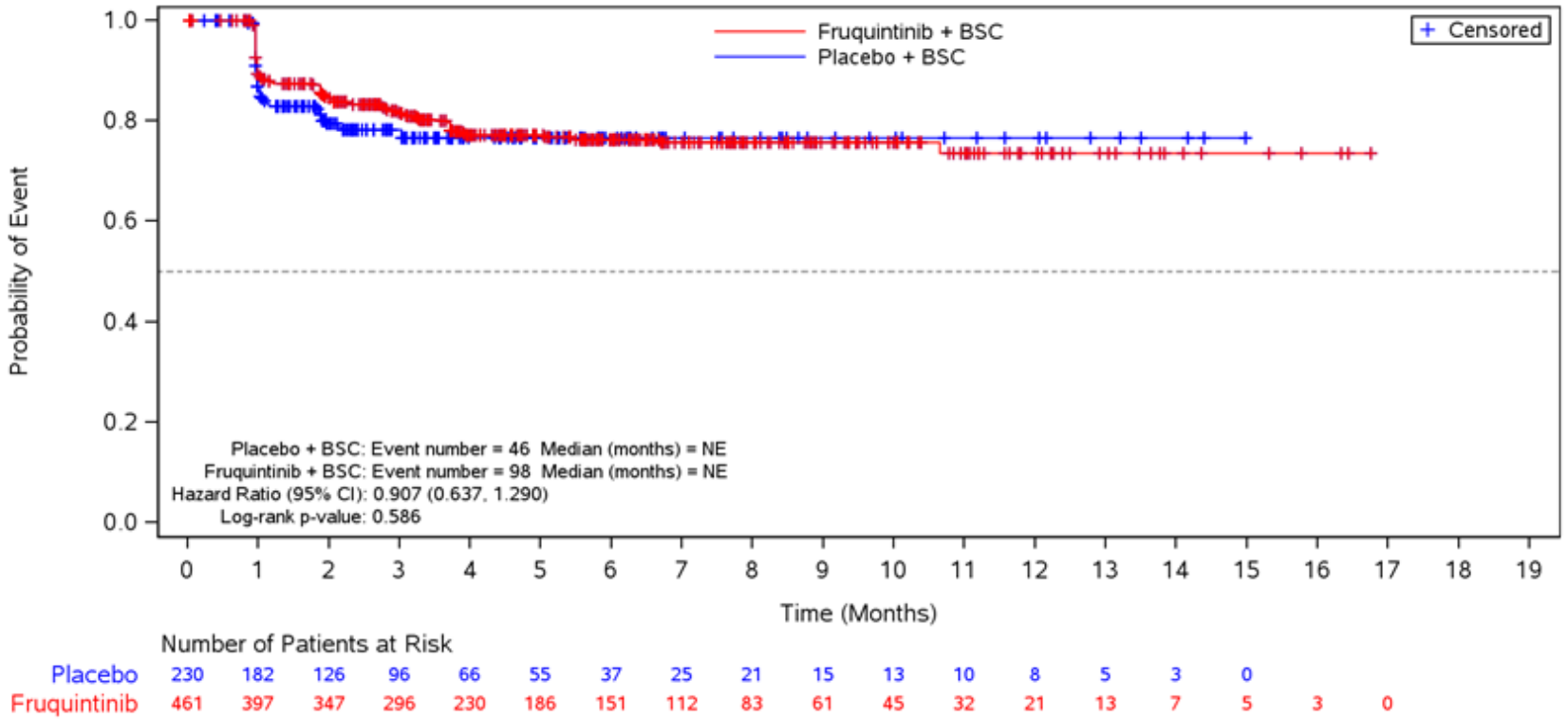
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Emotional Functioning



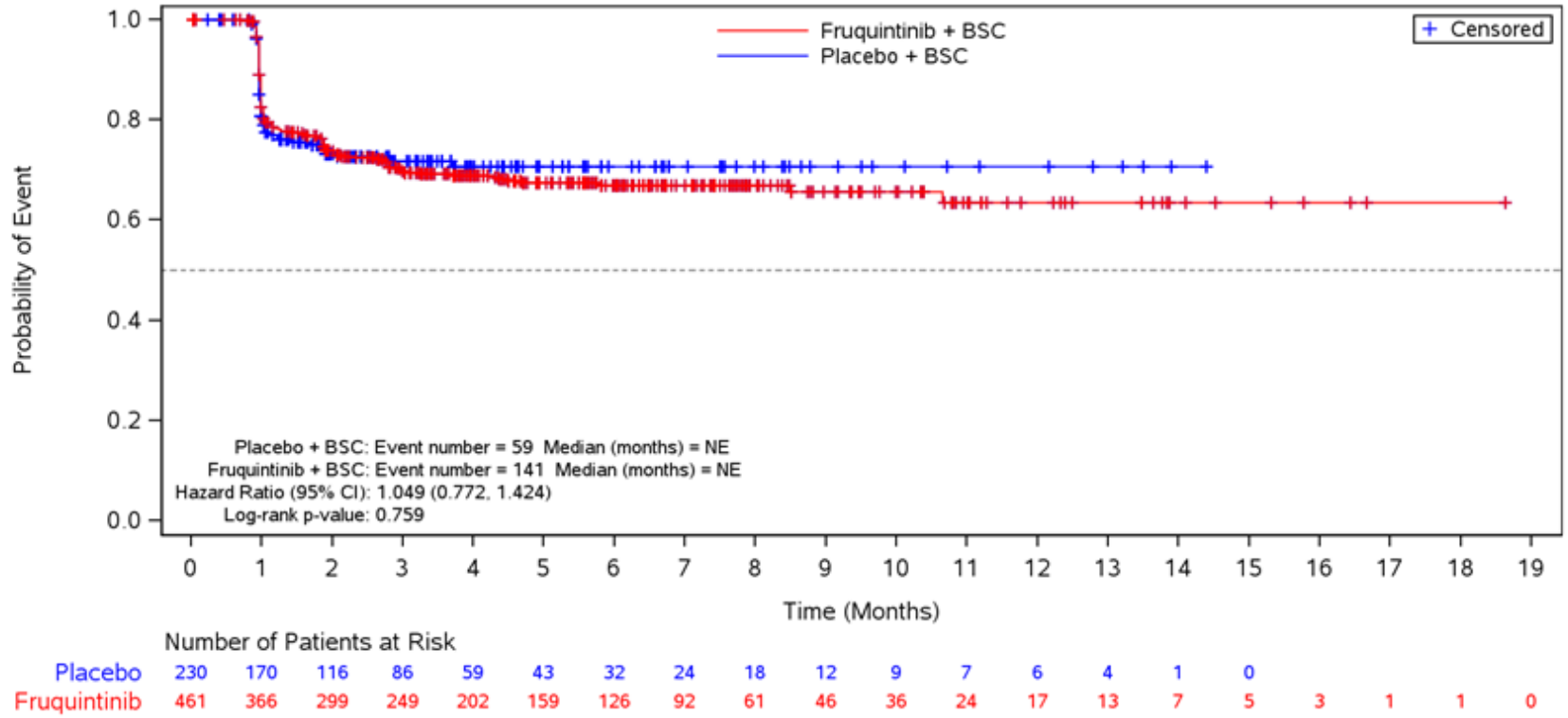
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Cognitive Functioning



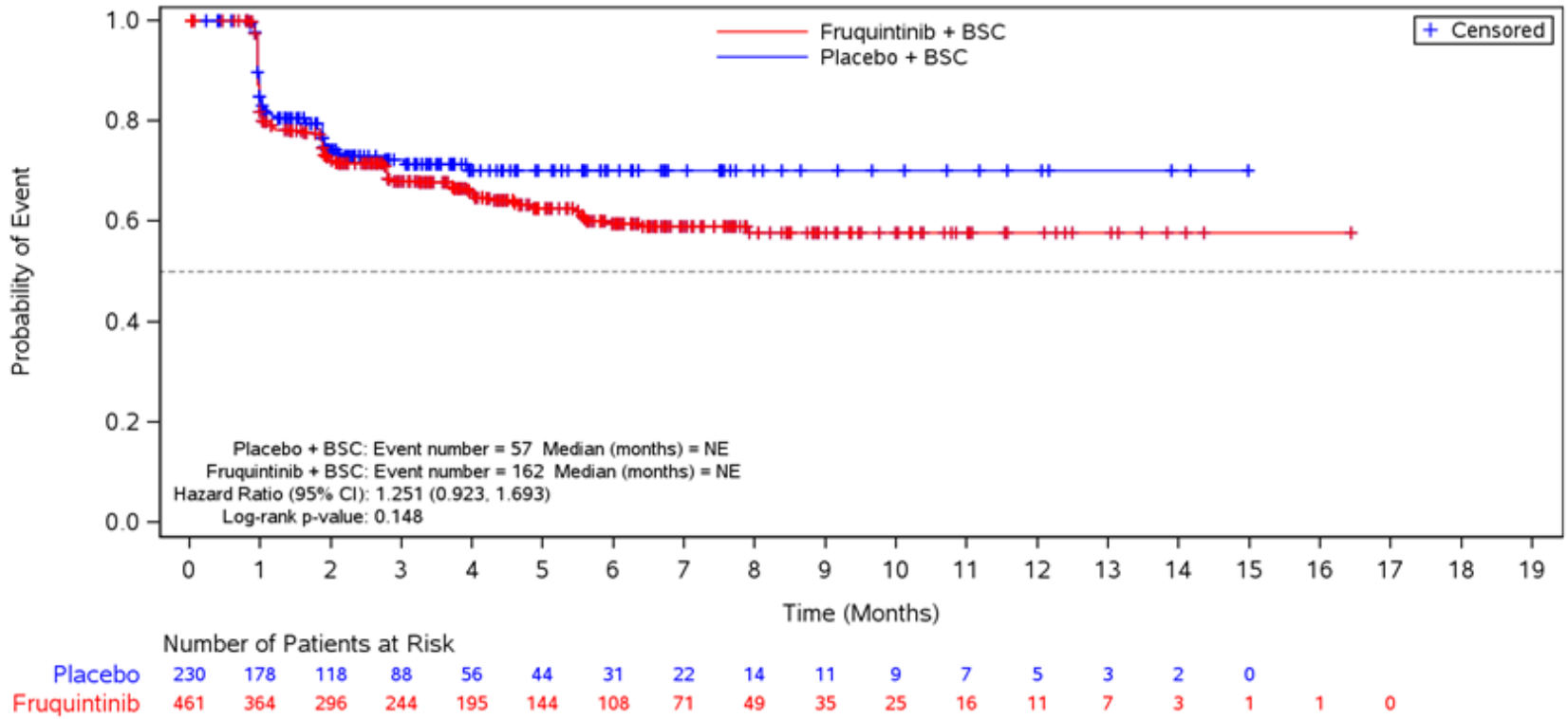
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Social Functioning



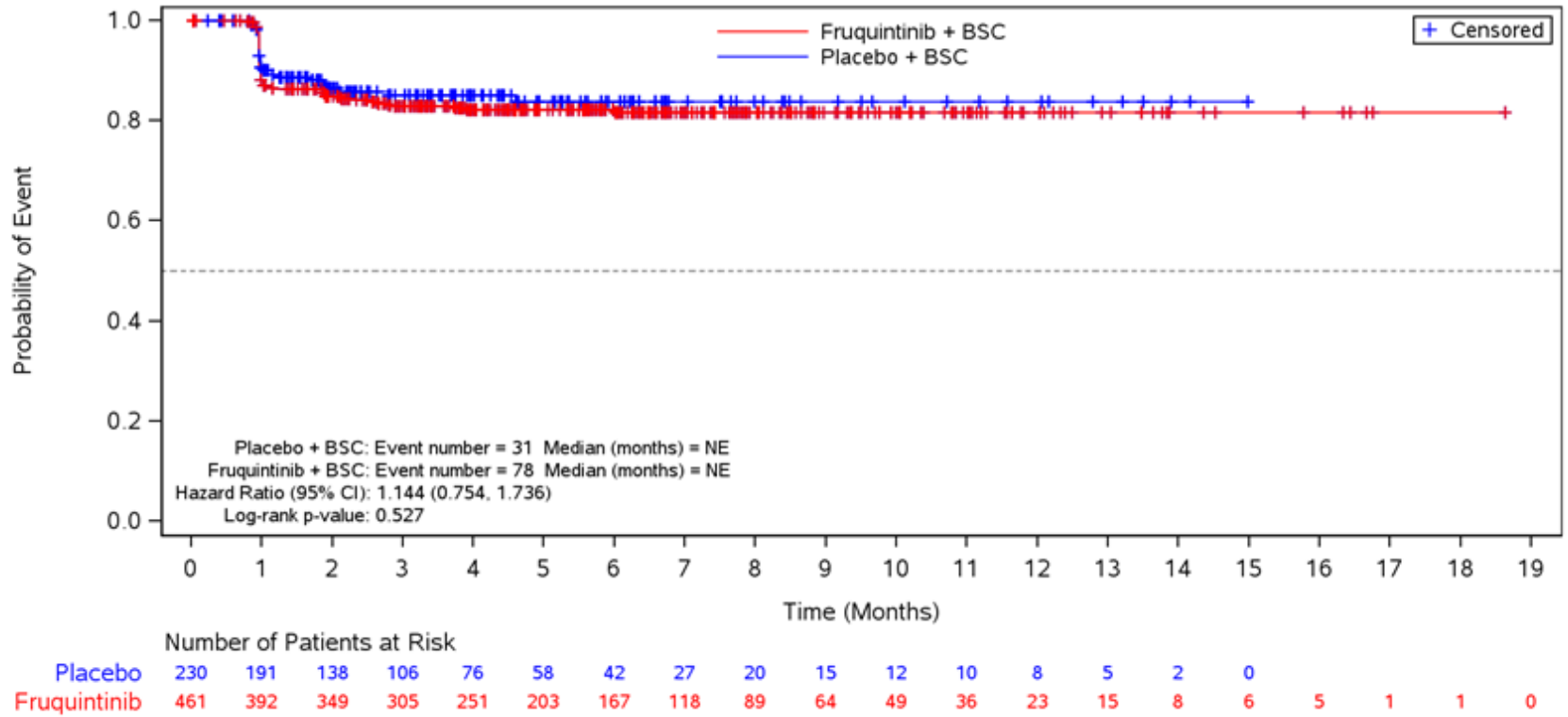
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Fatigue



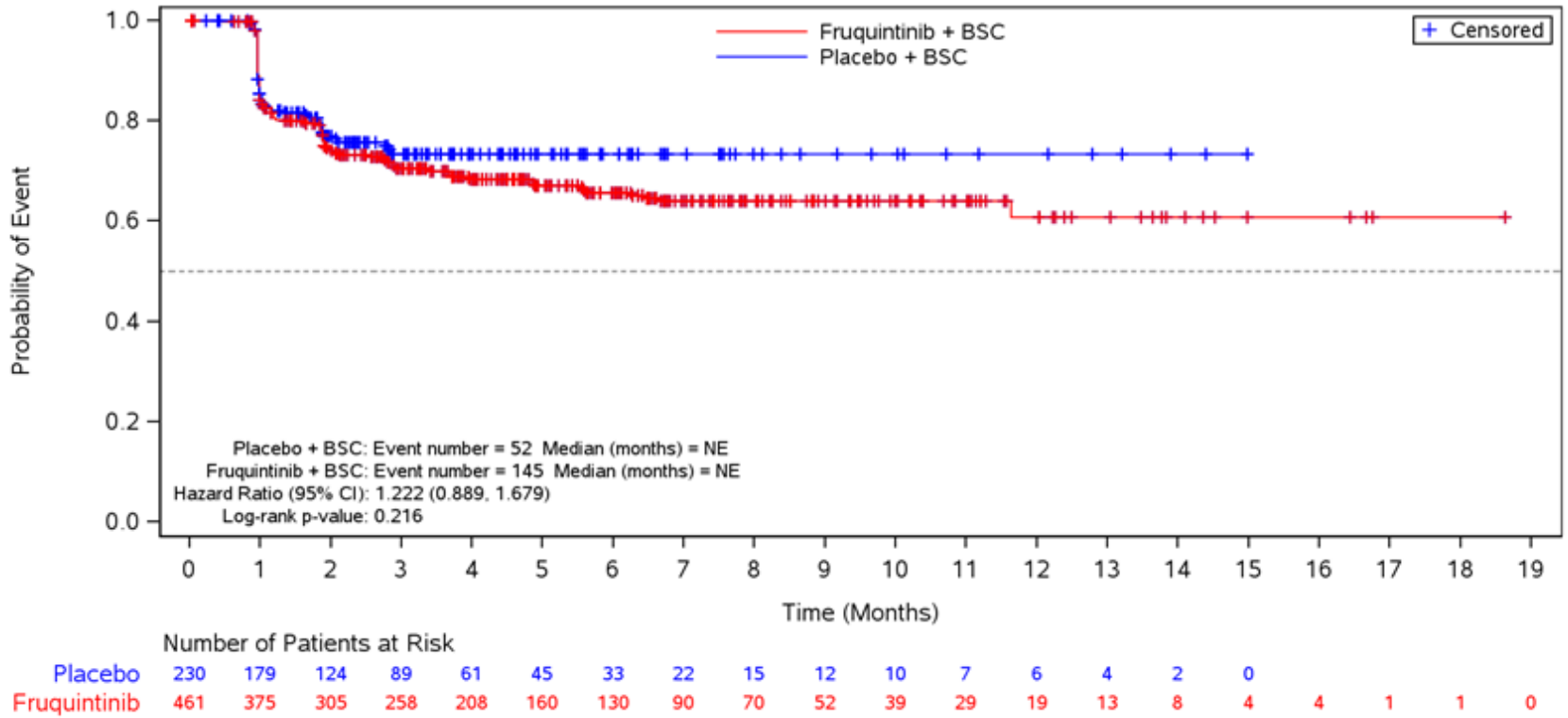
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Nausea and vomiting



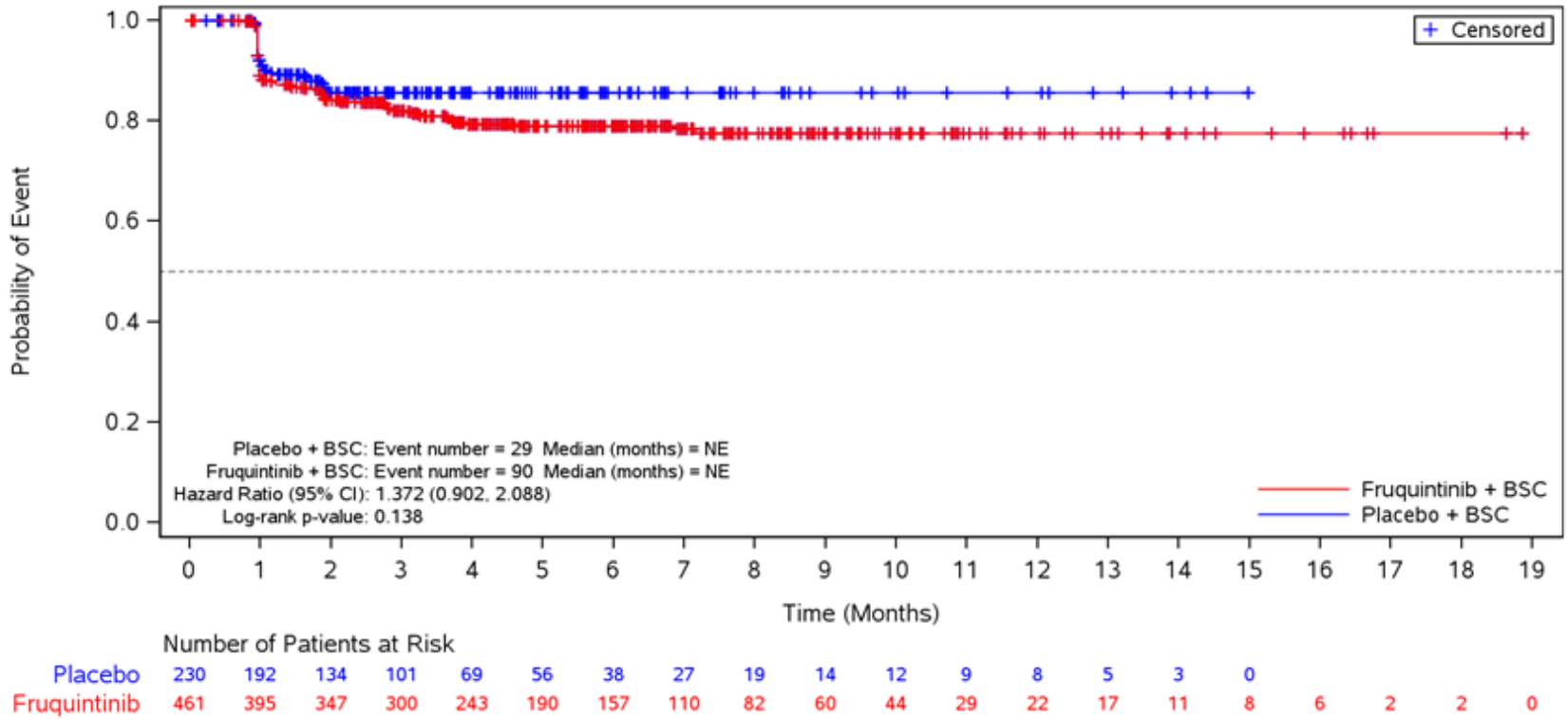
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Pain



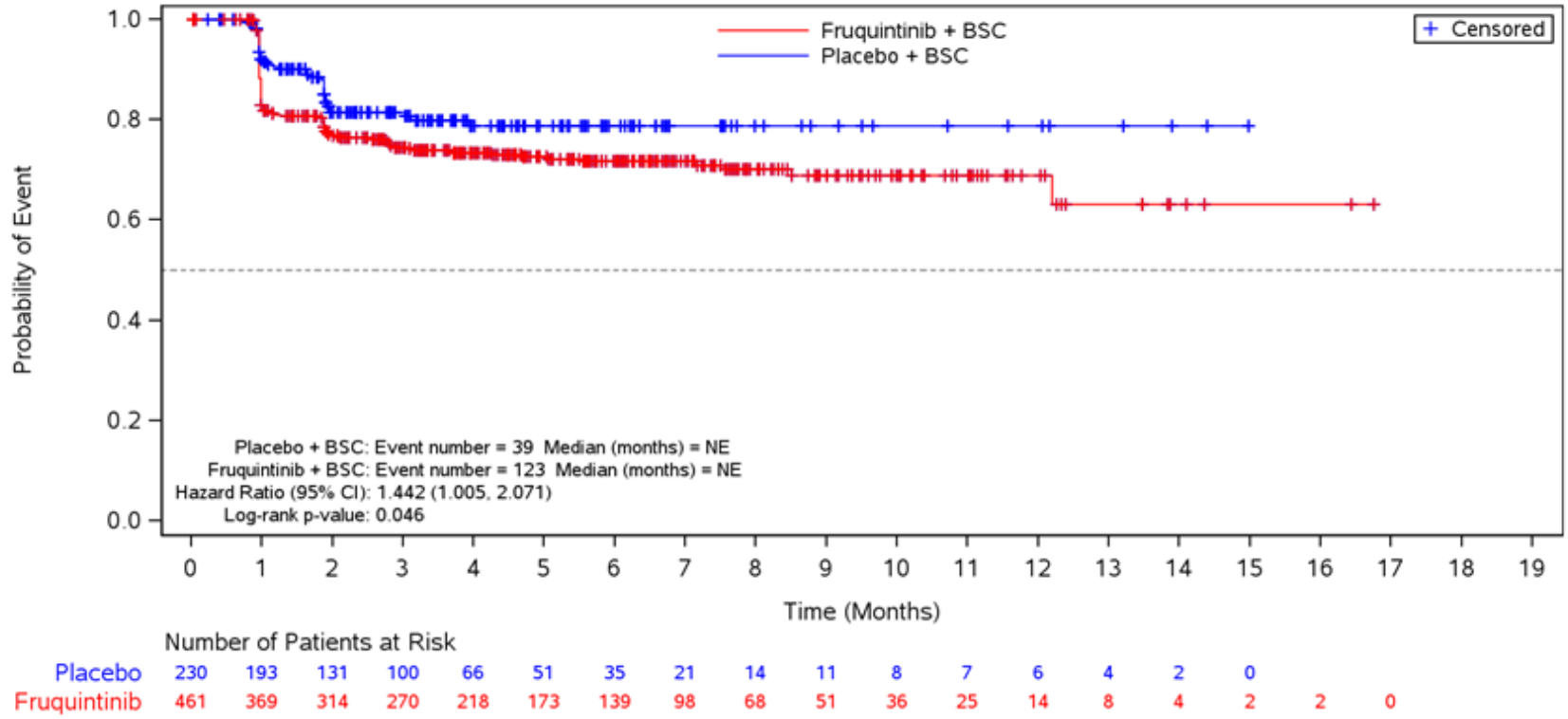
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Dyspnoea



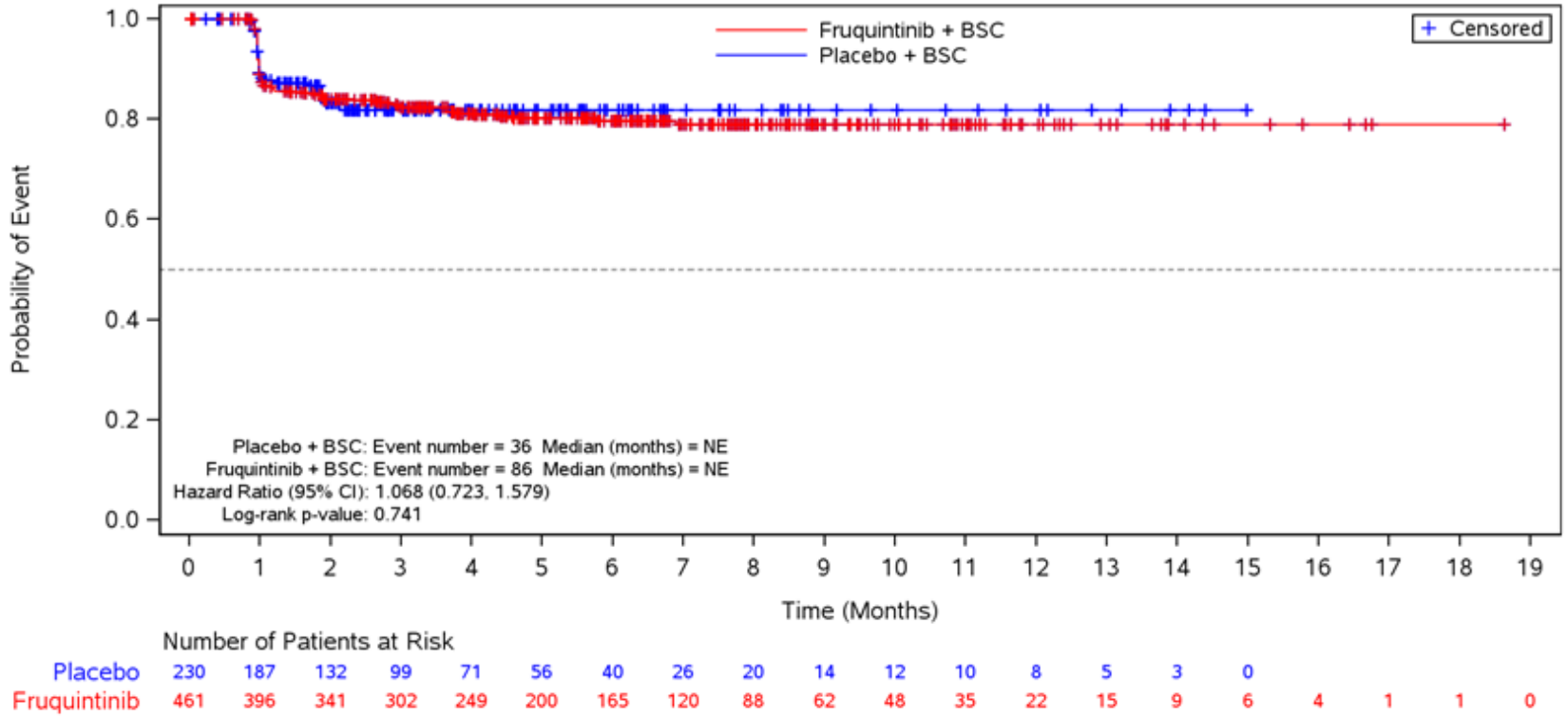
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Insomnia



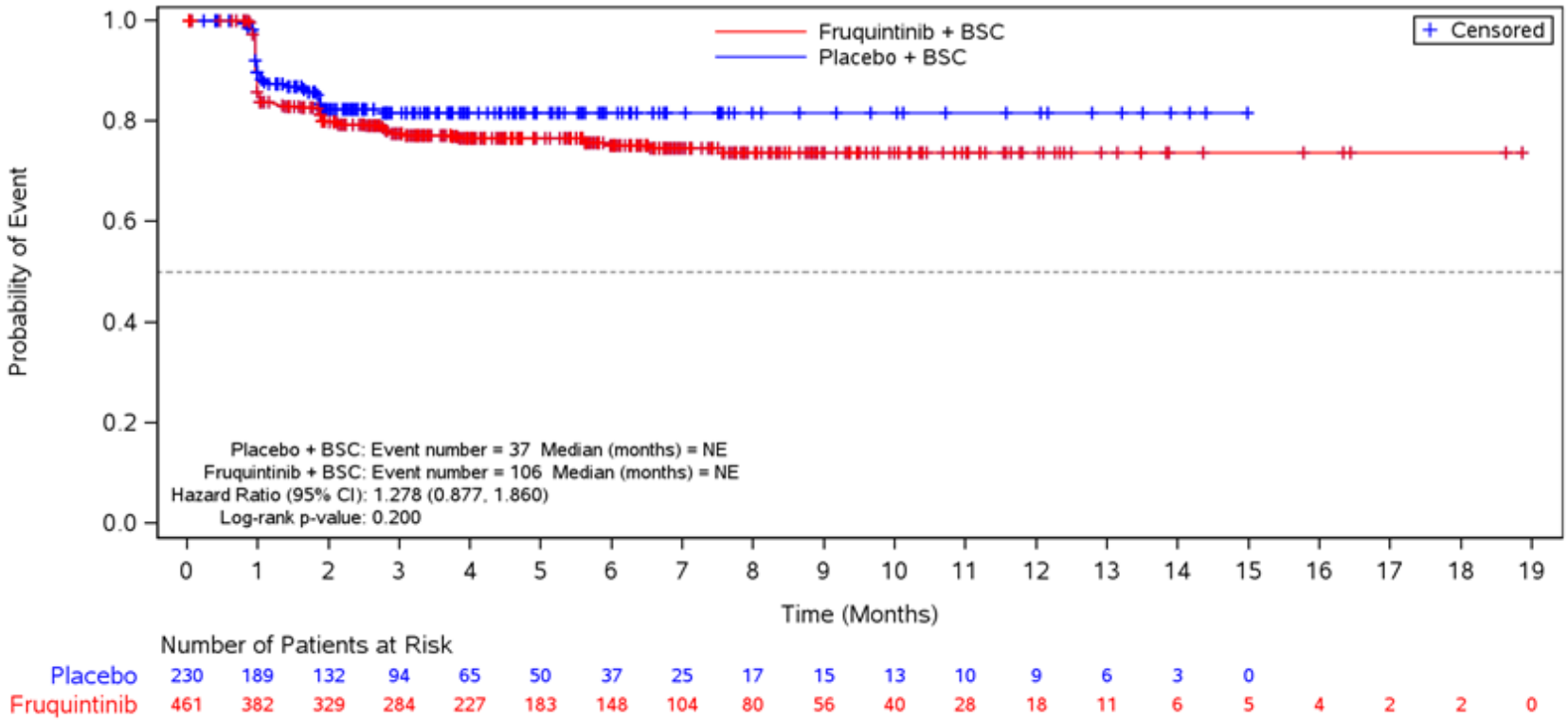
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Appetite loss



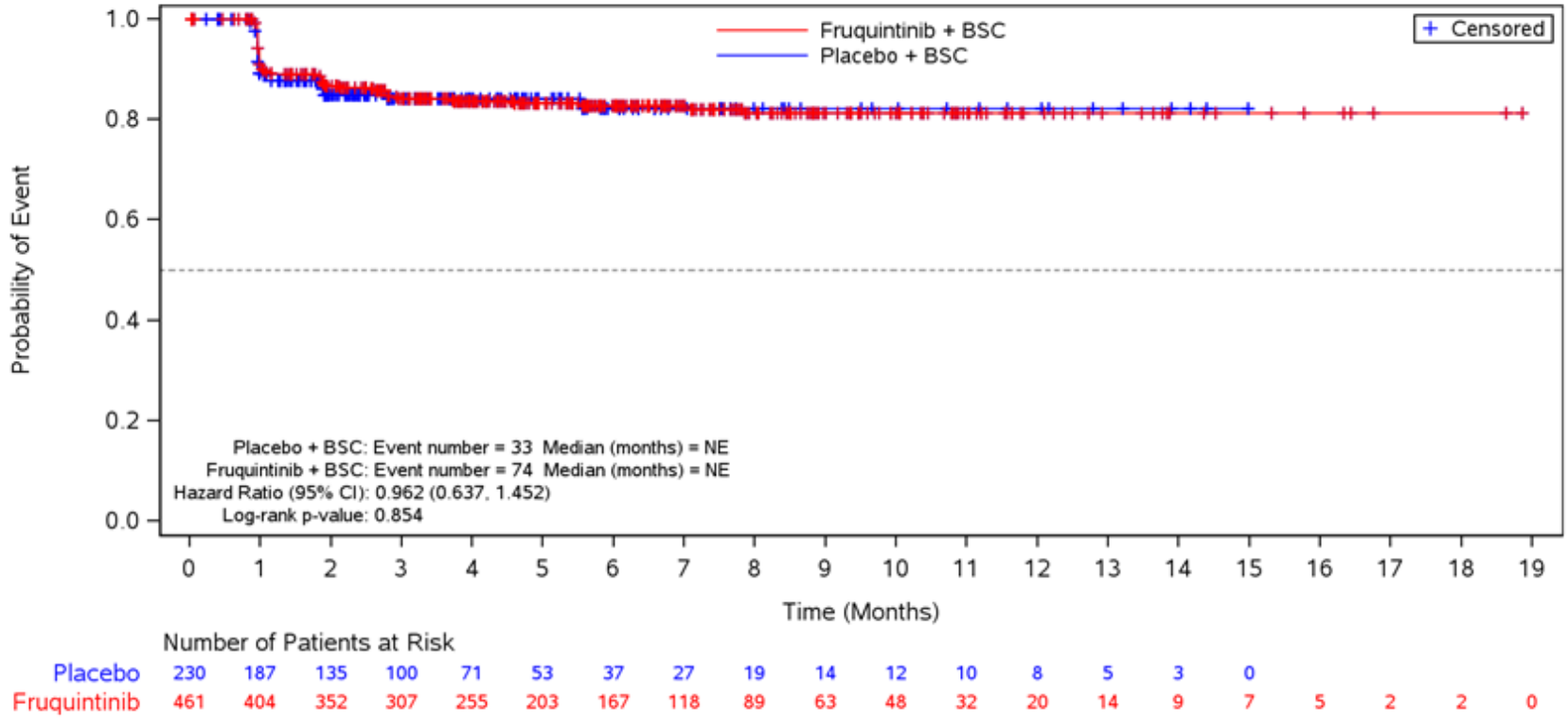
BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Constipation



BSC=Best supportive care.

Figure 35.1.1.4.4A
Kaplan-Meier Plot for Time to Improvement of EORTC QLQ-C30 V3.0
Intent-to-Treat Population
Diarrhoea



BSC=Best supportive care.

1.3.5 MMRM-Analyse

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	64.6 (19.71)	65.2 (19.90)
Median	66.7	66.7
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	63.3 (20.97)	64.1 (19.61)
Median	66.7	66.7
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	-4.7 (18.87)	-2.4 (19.36)
Median	0.0	0.0
Min, Max	-67, 67	-58, 58
LS Mean change from baseline (SE)	-3.7 (1.95)	-2.1 (1.59)
95% CI	(-7.5, 0.1)	(-5.2, 1.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.7 (1.69)
95% CI		(-1.7, 5.0)
P-value		0.327
Hedges's g		0.10 (-0.10, 0.29)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	66.0 (19.40)	63.3 (18.62)
Median	66.7	66.7
Min, Max	17, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	-6.8 (19.48)	-4.9 (19.77)
Median	0.0	0.0
Min, Max	-58, 50	-92, 50
LS Mean change from baseline (SE)	-6.1 (2.54)	-4.5 (1.69)
95% CI	(-11.1, -1.1)	(-7.8, -1.2)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.6 (2.46)
95% CI		(-3.2, 6.4)
P-value		0.517
Hedges's g		0.10 (-0.20, 0.40)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	71.1 (18.79)	64.0 (18.56)
Median	75.0	66.7
Min, Max	33, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-2.9 (15.31)	-4.2 (19.97)
Median	0.0	0.0
Min, Max	-42, 33	-67, 67
LS Mean change from baseline (SE)	-2.1 (3.03)	-4.2 (1.76)
95% CI	(-8.0, 3.9)	(-7.7, -0.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.2 (2.99)
95% CI		(-8.1, 3.7)
P-value		0.468
Hedges's g		-0.14 (-0.54, 0.25)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Global health status/QoL

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-3.6 (2.10)	-1.8 (1.74)
95% CI	(-7.7, 0.5)	(-5.2, 1.6)
LS Mean difference (Fruquintinib – Placebo) (SE)		1.8 (1.69)
95% CI		(-1.5, 5.1)
P-value		0.290
Hedges's g		0.10 (-0.09, 0.30)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	77.7 (19.11)	78.8 (18.85)
Median	80.0	86.7
Min, Max	7, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	77.5 (20.86)	75.1 (19.83)
Median	80.0	80.0
Min, Max	13, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	-3.6 (14.92)	-4.6 (15.65)
Median	0.0	0.0
Min, Max	-60, 40	-73, 60
LS Mean change from baseline (SE)	-3.5 (1.69)	-4.8 (1.38)
95% CI	(-6.8, -0.2)	(-7.5, -2.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.3 (1.44)
95% CI		(-4.2, 1.5)
P-value		0.358
Hedges's g		-0.09 (-0.28, 0.10)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	78.7 (19.87)	74.0 (19.72)
Median	86.7	80.0
Min, Max	27, 100	20, 100
Change from Baseline		
n	53	229
Mean (SD)	-2.1 (16.37)	-7.2 (16.30)
Median	0.0	-6.7
Min, Max	-47, 33	-60, 33
LS Mean change from baseline (SE)	-4.2 (2.26)	-7.1 (1.51)
95% CI	(-8.7, 0.2)	(-10.0, -4.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.9 (2.19)
95% CI		(-7.2, 1.4)
P-value		0.192
Hedges's g		-0.20 (-0.50, 0.10)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	76.0 (23.33)	73.3 (20.96)
Median	80.0	80.0
Min, Max	20, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-2.3 (10.58)	-7.6 (16.61)
Median	0.0	-6.7
Min, Max	-40, 13	-87, 40
LS Mean change from baseline (SE)	-6.8 (2.90)	-7.7 (1.61)
95% CI	(-12.5, -1.1)	(-10.9, -4.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-0.9 (2.90)
95% CI		(-6.6, 4.8)
P-value		0.752
Hedges's g		-0.06 (-0.45, 0.33)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Physical Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-3.7 (1.81)	-4.9 (1.50)
95% CI	(-7.3, -0.2)	(-7.9, -2.0)
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.2 (1.46)
95% CI		(-4.0, 1.7)
P-value		0.423
Hedges's g		-0.08 (-0.27, 0.11)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	72.7 (28.87)	75.8 (26.08)
Median	66.7	83.3
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	74.5 (27.18)	70.8 (26.36)
Median	83.3	66.7
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	-4.4 (25.73)	-5.9 (24.68)
Median	0.0	0.0
Min, Max	-67, 100	-83, 67
LS Mean change from baseline (SE)	-4.5 (2.50)	-7.0 (2.03)
95% CI	(-9.4, 0.4)	(-11.0, -3.0)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.5 (2.18)
95% CI		(-6.8, 1.7)
P-value		0.243
Hedges's g		-0.12 (-0.31, 0.08)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	78.3 (27.85)	70.2 (26.85)
Median	100.0	66.7
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	-5.7 (25.31)	-8.7 (24.01)
Median	0.0	0.0
Min, Max	-67, 67	-83, 67
LS Mean change from baseline (SE)	-5.1 (3.37)	-9.1 (2.19)
95% CI	(-11.8, 1.5)	(-13.4, -4.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-3.9 (3.29)
95% CI		(-10.4, 2.6)
P-value		0.235
Hedges's g		-0.18 (-0.48, 0.12)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	77.2 (32.01)	68.6 (27.82)
Median	100.0	66.7
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-3.4 (20.11)	-8.9 (27.40)
Median	0.0	0.0
Min, Max	-67, 33	-100, 83
LS Mean change from baseline (SE)	-6.1 (4.39)	-8.9 (2.38)
95% CI	(-14.8, 2.5)	(-13.6, -4.3)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.8 (4.41)
95% CI		(-11.5, 5.9)
P-value		0.525
Hedges's g		-0.13 (-0.52, 0.27)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Role Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-4.4 (2.72)	-6.7 (2.26)
95% CI	(-9.8, 0.9)	(-11.1, -2.2)
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.3 (2.19)
95% CI		(-6.6, 2.0)
P-value		0.299
Hedges's g		-0.10 (-0.30, 0.09)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	76.5 (21.35)	79.3 (19.30)
Median	83.3	83.3
Min, Max	8, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	77.6 (20.56)	81.1 (17.14)
Median	83.3	83.3
Min, Max	0, 100	8, 100
Change from Baseline		
n	149	330
Mean (SD)	-0.6 (17.22)	1.4 (17.34)
Median	0.0	0.0
Min, Max	-75, 83	-58, 67
LS Mean change from baseline (SE)	-1.5 (1.69)	1.3 (1.37)
95% CI	(-4.8, 1.8)	(-1.4, 4.0)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		2.8 (1.46)
95% CI		(-0.0, 5.7)
P-value		0.054
Hedges's g		0.19 (-0.00, 0.38)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	79.7 (20.31)	79.8 (17.52)
Median	83.3	83.3
Min, Max	0, 100	8, 100
Change from Baseline		
n	53	229
Mean (SD)	-0.8 (17.62)	-1.1 (19.05)
Median	0.0	0.0
Min, Max	-75, 42	-67, 67
LS Mean change from baseline (SE)	-0.3 (2.36)	-1.0 (1.52)
95% CI	(-4.9, 4.3)	(-4.0, 2.0)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-0.7 (2.32)
95% CI		(-5.2, 3.9)
P-value		0.774
Hedges's g		-0.04 (-0.34, 0.26)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	83.6 (19.63)	79.6 (18.01)
Median	91.7	83.3
Min, Max	25, 100	17, 100
Change from Baseline		
n	29	182
Mean (SD)	1.1 (17.21)	-0.8 (18.45)
Median	0.0	0.0
Min, Max	-50, 33	-50, 42
LS Mean change from baseline (SE)	2.7 (2.95)	-0.9 (1.61)
95% CI	(-3.1, 8.5)	(-4.1, 2.3)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-3.6 (2.96)
95% CI		(-9.4, 2.2)
P-value		0.225
Hedges's g		-0.24 (-0.63, 0.15)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Emotional Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-0.7 (1.83)	2.0 (1.51)
95% CI	(-4.3, 2.9)	(-1.0, 4.9)
LS Mean difference (Fruquintinib – Placebo) (SE)		2.7 (1.47)
95% CI		(-0.2, 5.6)
P-value		0.071
Hedges's g		0.18 (-0.02, 0.37)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	85.7 (17.59)	87.1 (16.90)
Median	83.3	100.0
Min, Max	33, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	85.0 (21.52)	85.1 (20.17)
Median	100.0	100.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	-2.6 (17.73)	-1.9 (14.98)
Median	0.0	0.0
Min, Max	-83, 50	-83, 50
LS Mean change from baseline (SE)	-4.7 (1.73)	-3.8 (1.40)
95% CI	(-8.1, -1.3)	(-6.6, -1.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		0.8 (1.52)
95% CI		(-2.1, 3.8)
P-value		0.578
Hedges's g		0.05 (-0.14, 0.25)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	84.3 (20.78)	82.6 (19.60)
Median	100.0	83.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	-2.2 (15.69)	-5.1 (16.76)
Median	0.0	0.0
Min, Max	-50, 50	-67, 33
LS Mean change from baseline (SE)	-5.3 (2.39)	-6.8 (1.53)
95% CI	(-10.0, -0.6)	(-9.8, -3.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.5 (2.35)
95% CI		(-6.2, 3.1)
P-value		0.518
Hedges's g		-0.10 (-0.40, 0.20)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	83.9 (24.17)	81.3 (20.71)
Median	100.0	83.3
Min, Max	0, 100	17, 100
Change from Baseline		
n	29	182
Mean (SD)	-1.7 (13.62)	-6.0 (18.13)
Median	0.0	0.0
Min, Max	-33, 17	-83, 33
LS Mean change from baseline (SE)	-4.8 (3.16)	-7.9 (1.67)
95% CI	(-11.0, 1.4)	(-11.1, -4.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-3.1 (3.19)
95% CI		(-9.3, 3.2)
P-value		0.340
Hedges's g		-0.19 (-0.58, 0.20)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Cognitive Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-3.9 (1.90)	-3.0 (1.57)
95% CI	(-7.6, -0.2)	(-6.1, 0.1)
LS Mean difference (Fruquintinib – Placebo) (SE)		0.9 (1.53)
95% CI		(-2.1, 3.9)
P-value		0.552
Hedges's g		0.06 (-0.13, 0.25)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	76.1 (26.72)	77.5 (24.90)
Median	83.3	83.3
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	82.4 (24.05)	79.6 (23.20)
Median	100.0	83.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	2.6 (21.02)	1.2 (24.68)
Median	0.0	0.0
Min, Max	-67, 67	-100, 83
LS Mean change from baseline (SE)	2.2 (2.26)	0.2 (1.83)
95% CI	(-2.2, 6.7)	(-3.4, 3.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.0 (1.98)
95% CI		(-5.9, 1.9)
P-value		0.313
Hedges's g		-0.10 (-0.29, 0.09)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	83.6 (24.35)	79.8 (22.76)
Median	100.0	83.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	2.2 (18.79)	-0.2 (24.21)
Median	0.0	0.0
Min, Max	-50, 50	-100, 100
LS Mean change from baseline (SE)	0.8 (3.00)	-1.3 (1.97)
95% CI	(-5.1, 6.7)	(-5.2, 2.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.1 (2.92)
95% CI		(-7.9, 3.6)
P-value		0.462
Hedges's g		-0.11 (-0.41, 0.19)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	81.1 (25.04)	76.7 (23.92)
Median	91.7	83.3
Min, Max	17, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-2.9 (23.60)	-2.6 (24.33)
Median	0.0	0.0
Min, Max	-67, 33	-83, 67
LS Mean change from baseline (SE)	-1.0 (4.09)	-3.7 (2.16)
95% CI	(-9.0, 7.1)	(-7.9, 0.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.7 (4.11)
95% CI		(-10.8, 5.4)
P-value		0.512
Hedges's g		-0.13 (-0.52, 0.26)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Social Functioning

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	2.7 (2.49)	0.8 (2.06)
95% CI	(-2.2, 7.6)	(-3.3, 4.8)
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.9 (2.00)
95% CI		(-5.9, 2.0)
P-value		0.334
Hedges's g		-0.10 (-0.29, 0.10)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	35.9 (25.49)	34.3 (22.46)
Median	33.3	33.3
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	35.4 (23.84)	38.6 (21.14)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	5.4 (19.91)	5.2 (21.19)
Median	0.0	0.0
Min, Max	-56, 78	-67, 67
LS Mean change from baseline (SE)	3.5 (2.07)	4.7 (1.69)
95% CI	(-0.5, 7.6)	(1.3, 8.0)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.1 (1.77)
95% CI		(-2.4, 4.6)
P-value		0.527
Hedges's g		0.06 (-0.13, 0.26)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	32.3 (22.88)	40.8 (22.96)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	5.0 (18.17)	9.5 (21.14)
Median	0.0	11.1
Min, Max	-33, 67	-56, 67
LS Mean change from baseline (SE)	4.6 (2.84)	8.5 (1.85)
95% CI	(-1.0, 10.2)	(4.8, 12.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		3.9 (2.78)
95% CI		(-1.6, 9.3)
P-value		0.166
Hedges's g		0.21 (-0.09, 0.51)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	31.9 (26.06)	40.3 (24.03)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	5.7 (20.49)	7.9 (22.43)
Median	0.0	0.0
Min, Max	-33, 67	-56, 78
LS Mean change from baseline (SE)	5.9 (3.71)	7.5 (2.02)
95% CI	(-1.4, 13.2)	(3.5, 11.4)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.6 (3.74)
95% CI		(-5.8, 9.0)
P-value		0.672
Hedges's g		0.08 (-0.31, 0.48)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Fatigue

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	2.6 (2.22)	3.8 (1.84)
95% CI	(-1.7, 7.0)	(0.2, 7.4)
LS Mean difference (Fruquintinib – Placebo) (SE)		1.2 (1.79)
95% CI		(-2.3, 4.7)
P-value		0.513
Hedges's g		0.06 (-0.13, 0.26)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	8.4 (15.89)	7.8 (15.84)
Median	0.0	0.0
Min, Max	0, 83	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	8.6 (15.31)	5.7 (12.94)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	149	330
Mean (SD)	2.1 (14.54)	-1.3 (17.17)
Median	0.0	0.0
Min, Max	-33, 67	-100, 83
LS Mean change from baseline (SE)	1.2 (1.51)	-1.5 (1.23)
95% CI	(-1.8, 4.2)	(-3.9, 0.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.7 (1.29)
95% CI		(-5.2, -0.2)
P-value		0.038
Hedges's g		-0.21 (-0.40, -0.01)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	8.8 (19.78)	7.4 (12.88)
Median	0.0	0.0
Min, Max	0, 100	0, 67
Change from Baseline		
n	53	229
Mean (SD)	3.5 (14.75)	0.3 (18.99)
Median	0.0	0.0
Min, Max	-33, 50	-100, 67
LS Mean change from baseline (SE)	3.1 (2.09)	0.2 (1.36)
95% CI	(-1.0, 7.2)	(-2.4, 2.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.9 (2.04)
95% CI		(-6.9, 1.2)
P-value		0.163
Hedges's g		-0.21 (-0.51, 0.09)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	6.7 (11.24)	8.4 (17.60)
Median	0.0	0.0
Min, Max	0, 33	0, 100
Change from Baseline		
n	29	182
Mean (SD)	1.1 (9.89)	1.6 (19.09)
Median	0.0	0.0
Min, Max	-33, 33	-100, 100
LS Mean change from baseline (SE)	1.0 (2.86)	1.6 (1.52)
95% CI	(-4.6, 6.6)	(-1.4, 4.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		0.6 (2.89)
95% CI		(-5.1, 6.3)
P-value		0.846
Hedges's g		0.04 (-0.35, 0.43)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Nausea and vomiting

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	1.3 (1.62)	-1.6 (1.34)
95% CI	(-1.9, 4.5)	(-4.2, 1.1)
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.8 (1.30)
95% CI		(-5.4, -0.3)
P-value		0.030
Hedges's g		-0.21 (-0.41, -0.02)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	29.8 (27.69)	27.4 (25.08)
Median	16.7	16.7
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	29.7 (26.21)	30.8 (23.13)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	4.7 (23.81)	4.0 (24.45)
Median	0.0	0.0
Min, Max	-100, 83	-67, 83
LS Mean change from baseline (SE)	5.1 (2.33)	5.3 (1.90)
95% CI	(0.6, 9.7)	(1.6, 9.0)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		0.2 (2.00)
95% CI		(-3.8, 4.1)
P-value		0.935
Hedges's g		0.01 (-0.19, 0.20)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	29.9 (26.42)	29.6 (24.48)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	7.5 (23.70)	5.9 (24.54)
Median	0.0	0.0
Min, Max	-33, 67	-67, 67
LS Mean change from baseline (SE)	8.7 (3.11)	6.5 (2.07)
95% CI	(2.6, 14.8)	(2.4, 10.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.3 (3.02)
95% CI		(-8.2, 3.7)
P-value		0.456
Hedges's g		-0.11 (-0.41, 0.19)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	26.7 (27.54)	31.7 (25.01)
Median	25.0	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	5.2 (24.03)	7.4 (26.01)
Median	0.0	0.0
Min, Max	-33, 67	-50, 100
LS Mean change from baseline (SE)	5.5 (4.10)	7.8 (2.24)
95% CI	(-2.6, 13.6)	(3.4, 12.2)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		2.3 (4.11)
95% CI		(-5.8, 10.4)
P-value		0.574
Hedges's g		0.11 (-0.28, 0.50)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Pain

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	3.8 (2.50)	4.0 (2.07)
95% CI	(-1.1, 8.7)	(-0.1, 8.1)
LS Mean difference (Fruquintinib – Placebo) (SE)		0.2 (2.01)
95% CI		(-3.7, 4.2)
P-value		0.914
Hedges's g		0.01 (-0.18, 0.20)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	20.9 (26.91)	18.8 (25.50)
Median	0.0	0.0
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	20.5 (23.92)	18.9 (22.74)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	2.9 (23.87)	0.6 (23.24)
Median	0.0	0.0
Min, Max	-67, 100	-100, 67
LS Mean change from baseline (SE)	3.1 (2.24)	0.9 (1.83)
95% CI	(-1.3, 7.5)	(-2.7, 4.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.2 (1.92)
95% CI		(-6.0, 1.5)
P-value		0.241
Hedges's g		-0.12 (-0.31, 0.08)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	20.8 (24.66)	19.6 (23.31)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	53	229
Mean (SD)	8.8 (25.45)	3.8 (21.75)
Median	0.0	0.0
Min, Max	-33, 67	-67, 67
LS Mean change from baseline (SE)	7.1 (2.97)	2.6 (1.98)
95% CI	(1.2, 12.9)	(-1.3, 6.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-4.4 (2.87)
95% CI		(-10.1, 1.2)
P-value		0.123
Hedges's g		-0.24 (-0.53, 0.06)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	23.3 (30.51)	19.5 (24.39)
Median	16.7	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	4.6 (34.18)	0.9 (26.78)
Median	0.0	0.0
Min, Max	-67, 100	-100, 100
LS Mean change from baseline (SE)	8.4 (4.23)	0.2 (2.25)
95% CI	(0.0, 16.7)	(-4.2, 4.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-8.2 (4.28)
95% CI		(-16.6, 0.3)
P-value		0.058
Hedges's g		-0.38 (-0.77, 0.01)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Dyspnoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	2.7 (2.41)	0.4 (1.99)
95% CI	(-2.0, 7.4)	(-3.5, 4.3)
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.3 (1.94)
95% CI		(-6.1, 1.5)
P-value		0.237
Hedges's g		-0.12 (-0.31, 0.08)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	26.4 (30.23)	24.8 (28.50)
Median	33.3	33.3
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	27.2 (29.48)	21.9 (25.38)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	5.4 (23.27)	-3.6 (28.12)
Median	0.0	0.0
Min, Max	-67, 67	-100, 100
LS Mean change from baseline (SE)	7.2 (2.53)	-0.4 (2.05)
95% CI	(2.3, 12.2)	(-4.4, 3.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-7.6 (2.20)
95% CI		(-11.9, -3.3)
P-value		<.001
Hedges's g		-0.34 (-0.54, -0.15)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	25.2 (28.42)	24.8 (27.08)
Median	33.3	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	1.9 (30.95)	1.0 (27.82)
Median	0.0	0.0
Min, Max	-67, 67	-100, 100
LS Mean change from baseline (SE)	6.7 (3.52)	4.3 (2.26)
95% CI	(-0.2, 13.7)	(-0.1, 8.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-2.4 (3.47)
95% CI		(-9.3, 4.4)
P-value		0.482
Hedges's g		-0.11 (-0.41, 0.19)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	21.1 (29.66)	28.0 (27.65)
Median	0.0	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-1.1 (27.43)	3.1 (28.62)
Median	0.0	0.0
Min, Max	-67, 67	-100, 100
LS Mean change from baseline (SE)	1.1 (4.56)	7.1 (2.43)
95% CI	(-7.9, 10.1)	(2.3, 11.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		6.0 (4.59)
95% CI		(-3.0, 15.1)
P-value		0.190
Hedges's g		0.26 (-0.13, 0.65)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Insomnia

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	6.2 (2.75)	-1.1 (2.27)
95% CI	(0.8, 11.6)	(-5.6, 3.4)
LS Mean difference (Fruquintinib – Placebo) (SE)		-7.3 (2.21)
95% CI		(-11.7, -3.0)
P-value		<.001
Hedges's g		-0.33 (-0.52, -0.13)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	24.1 (28.46)	22.8 (28.90)
Median	0.0	0.0
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	24.0 (29.23)	23.2 (27.01)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	4.3 (25.49)	2.3 (28.91)
Median	0.0	0.0
Min, Max	-67, 100	-100, 100
LS Mean change from baseline (SE)	4.2 (2.79)	3.1 (2.29)
95% CI	(-1.2, 9.7)	(-1.4, 7.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.1 (2.38)
95% CI		(-5.8, 3.5)
P-value		0.634
Hedges's g		-0.05 (-0.24, 0.15)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	17.0 (25.84)	25.7 (29.60)
Median	0.0	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	6.9 (29.50)	8.2 (26.15)
Median	0.0	0.0
Min, Max	-67, 100	-100, 100
LS Mean change from baseline (SE)	5.0 (3.64)	8.1 (2.46)
95% CI	(-2.2, 12.1)	(3.2, 12.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		3.1 (3.49)
95% CI		(-3.8, 10.0)
P-value		0.373
Hedges's g		0.14 (-0.16, 0.43)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	22.2 (26.74)	26.8 (32.17)
Median	16.7	33.3
Min, Max	0, 100	0, 100
Change from Baseline		
n	29	182
Mean (SD)	13.8 (26.00)	10.4 (29.44)
Median	0.0	0.0
Min, Max	-33, 100	-100, 100
LS Mean change from baseline (SE)	9.3 (5.01)	10.6 (2.73)
95% CI	(-0.5, 19.2)	(5.2, 15.9)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.3 (5.04)
95% CI		(-8.7, 11.2)
P-value		0.804
Hedges's g		0.05 (-0.34, 0.44)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Appetite loss

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	2.9 (2.98)	1.8 (2.47)
95% CI	(-3.0, 8.7)	(-3.1, 6.6)
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.1 (2.40)
95% CI		(-5.8, 3.6)
P-value		0.644
Hedges's g		-0.05 (-0.24, 0.15)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	18.4 (27.93)	17.5 (25.78)
Median	0.0	0.0
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	18.5 (27.54)	16.1 (25.43)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	1.1 (28.58)	-0.6 (27.13)
Median	0.0	0.0
Min, Max	-100, 100	-67, 100
LS Mean change from baseline (SE)	-0.8 (2.62)	-2.6 (2.12)
95% CI	(-5.9, 4.4)	(-6.7, 1.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.8 (2.33)
95% CI		(-6.4, 2.8)
P-value		0.441
Hedges's g		-0.08 (-0.27, 0.12)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	15.7 (24.98)	16.5 (25.13)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	0.6 (24.01)	0.1 (24.48)
Median	0.0	0.0
Min, Max	-67, 67	-67, 100
LS Mean change from baseline (SE)	-0.5 (3.27)	-1.6 (2.19)
95% CI	(-6.9, 5.9)	(-5.9, 2.7)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.0 (3.13)
95% CI		(-7.2, 5.1)
P-value		0.740
Hedges's g		-0.05 (-0.35, 0.25)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	11.1 (20.22)	19.7 (27.39)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	29	182
Mean (SD)	3.4 (18.57)	2.9 (27.43)
Median	0.0	0.0
Min, Max	-33, 67	-67, 100
LS Mean change from baseline (SE)	0.4 (4.47)	1.7 (2.43)
95% CI	(-8.4, 9.2)	(-3.1, 6.5)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		1.3 (4.48)
95% CI		(-7.6, 10.1)
P-value		0.779
Hedges's g		0.06 (-0.34, 0.45)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Constipation

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-2.2 (2.90)	-3.9 (2.40)
95% CI	(-7.9, 3.5)	(-8.6, 0.8)
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.7 (2.33)
95% CI		(-6.3, 2.9)
P-value		0.463
Hedges's g		-0.07 (-0.27, 0.12)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	12.6 (22.80)	12.1 (22.28)
Median	0.0	0.0
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	9.6 (20.11)	13.6 (21.94)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	-1.6 (19.89)	2.2 (21.94)
Median	0.0	0.0
Min, Max	-67, 100	-67, 100
LS Mean change from baseline (SE)	-1.5 (2.11)	2.4 (1.70)
95% CI	(-5.7, 2.6)	(-1.0, 5.7)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		3.9 (1.85)
95% CI		(0.2, 7.5)
P-value		0.037
Hedges's g		0.21 (0.01, 0.40)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	7.5 (18.07)	14.0 (21.78)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	53	229
Mean (SD)	0.0 (20.67)	3.3 (23.23)
Median	0.0	0.0
Min, Max	-67, 67	-100, 100
LS Mean change from baseline (SE)	-1.9 (3.01)	3.4 (1.89)
95% CI	(-7.8, 4.0)	(-0.3, 7.1)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		5.3 (2.99)
95% CI		(-0.6, 11.2)
P-value		0.077
Hedges's g		0.27 (-0.03, 0.57)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	8.9 (17.36)	15.5 (23.36)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	29	182
Mean (SD)	-3.4 (16.29)	5.1 (25.71)
Median	0.0	0.0
Min, Max	-33, 33	-67, 100
LS Mean change from baseline (SE)	-2.3 (4.02)	4.3 (2.08)
95% CI	(-10.2, 5.6)	(0.2, 8.4)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		6.6 (4.08)
95% CI		(-1.4, 14.7)
P-value		0.105
Hedges's g		0.32 (-0.07, 0.72)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Diarrhoea

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	-2.6 (2.31)	1.3 (1.91)
95% CI	(-7.1, 2.0)	(-2.4, 5.1)
LS Mean difference (Fruquintinib – Placebo) (SE)		3.9 (1.86)
95% CI		(0.2, 7.5)
P-value		0.036
Hedges's g		0.21 (0.01, 0.40)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Baseline		
n	217	420
Mean (SD)	12.3 (23.19)	14.3 (24.53)
Median	0.0	0.0
Min, Max	0, 100	0, 100

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 2 Day 1		
n	153	357
Mean (SD)	10.9 (23.52)	12.3 (21.29)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	149	330
Mean (SD)	1.3 (17.28)	-1.9 (24.92)
Median	0.0	0.0
Min, Max	-67, 67	-100, 100
LS Mean change from baseline (SE)	0.9 (2.20)	0.3 (1.80)
95% CI	(-3.4, 5.2)	(-3.3, 3.8)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-0.6 (1.89)
95% CI		(-4.3, 3.1)
P-value		0.738
Hedges's g		-0.03 (-0.23, 0.16)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 3 Day 1		
n	53	253
Mean (SD)	11.9 (27.03)	14.2 (23.18)
Median	0.0	0.0
Min, Max	0, 100	0, 100
Change from Baseline		
n	53	229
Mean (SD)	5.0 (20.04)	-0.3 (25.17)
Median	0.0	0.0
Min, Max	-33, 100	-100, 100
LS Mean change from baseline (SE)	3.4 (3.04)	2.4 (1.99)
95% CI	(-2.5, 9.4)	(-1.5, 6.3)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.1 (2.97)
95% CI		(-6.9, 4.8)
P-value		0.723
Hedges's g		-0.05 (-0.35, 0.24)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Cycle 4 Day 1		
n	30	200
Mean (SD)	13.3 (22.49)	15.2 (23.58)
Median	0.0	0.0
Min, Max	0, 67	0, 100
Change from Baseline		
n	29	182
Mean (SD)	8.0 (19.22)	0.4 (26.68)
Median	0.0	0.0
Min, Max	-33, 67	-100, 100
LS Mean change from baseline (SE)	4.8 (4.08)	3.3 (2.17)
95% CI	(-3.2, 12.8)	(-0.9, 7.6)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
LS Mean difference (Fruquintinib – Placebo) (SE)		-1.5 (4.11)
95% CI		(-9.6, 6.6)
P-value		0.722
Hedges's g		-0.07 (-0.46, 0.32)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

Table 35.1.1.4.2A
MMRM Analysis of EORTC QLQ-C30 V3.0 Over Time
Intent-to-Treat Population
Subscale: Financial Difficulty

	Placebo + BSC N=230	Fruquintinib + BSC N=461
Overall (70% compliance)		
n	149	330
LS Mean change from baseline (SE)	1.4 (2.37)	0.7 (1.96)
95% CI	(-3.2, 6.1)	(-3.2, 4.5)
LS Mean difference (Fruquintinib – Placebo) (SE)		-0.8 (1.91)
95% CI		(-4.5, 3.0)
P-value		0.694
Hedges's g		-0.04 (-0.23, 0.15)

Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.

Hedges's g measures the effect size of the difference between means using results from mixed model.

The restricted maximum likelihood (REML)-based MMRM model includes treatment group, visit (i.e. cycle), treatment group by visit interaction, baseline value of the parameter, and randomization schedule stratification factors as fixed effects. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Unstructured covariance model does not converge, so the EMPIRICAL (CS type) option in the PROC MIXED statement in SAS was used.

BSC=Best standard care; MMRM=Mixed model repeated measures; LS=Least square.

1.4 Q-TWiST-Analyse

Table 35.1.1.9.1
Summary of Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis
ITT Population

	Placebo + BSC N=230	Fruquintinib 5mg + BSC N=461	Difference (Fruquintinib 5mg + BSC) - (Placebo + BSC)
Duration of health states (months)			
OS			
Mean (95% CI)	6.49 (5.82, 7.17)	8.44 (7.95, 8.93)	1.94 (1.11, 2.78)
p-value			< 0.05
PFS			
Mean (95% CI)	2.14 (1.95, 2.32)	4.51 (4.20, 4.82)	2.37 (2.01, 2.73)
p-value			< 0.05
Q-TWiST			
Mean (95% CI)	4.21 (3.81, 4.60)	6.25 (5.89, 6.61)	2.04 (1.51, 2.57)
p-value			< 0.05
TWiST			
Mean (95% CI)	1.92 (1.75, 2.10)	4.06 (3.75, 4.36)	2.14 (1.78, 2.49)
p-value			< 0.05
TOX			
Mean (95% CI)	0.21 (0.15, 0.28)	0.45 (0.37, 0.53)	0.24 (0.13, 0.34)
p-value			< 0.05

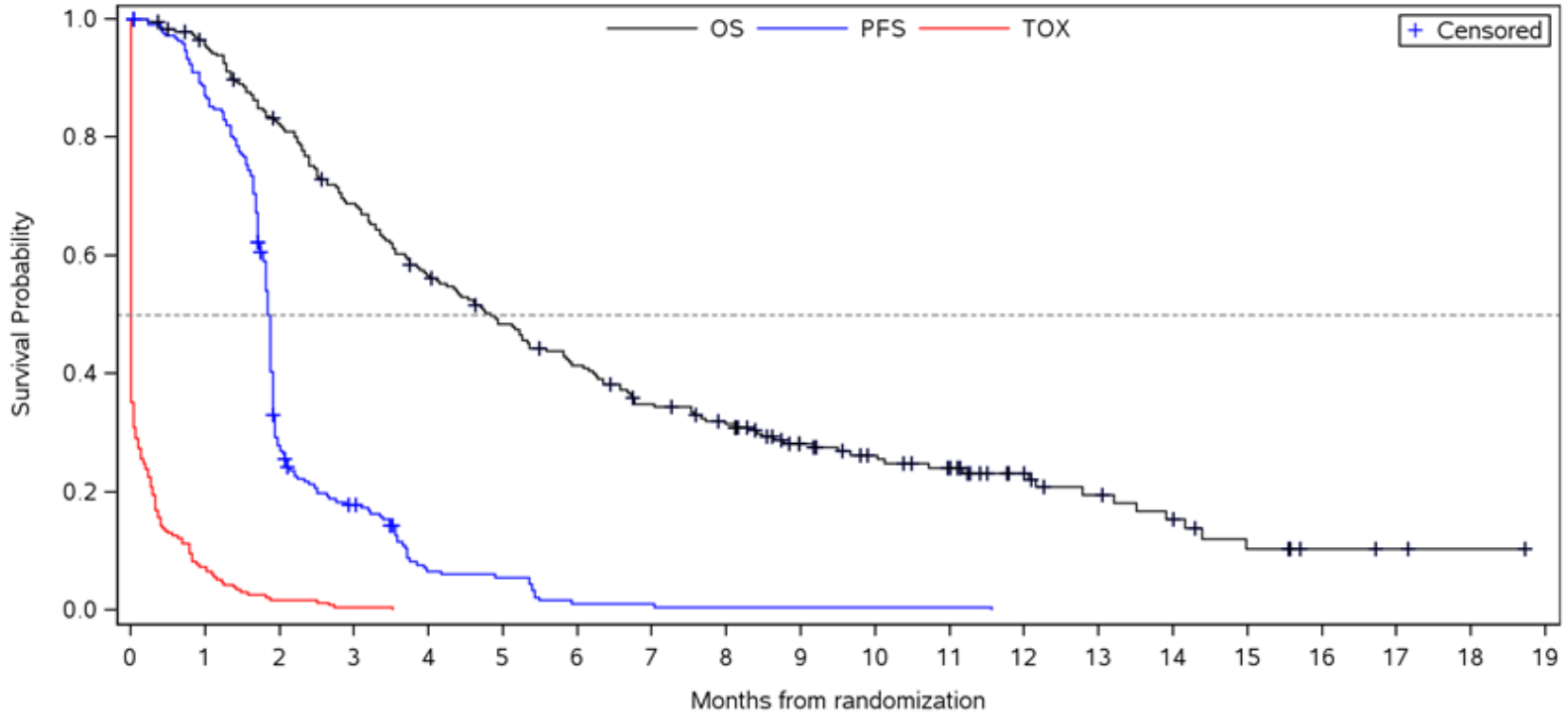
BSC: Best supportive care; Q-TWiST: Quality-adjusted time without symptoms or toxicity; REL: Relapse; TOX: Time of toxicity; TWiST: Time without symptoms or toxicity.
Mean durations of health states were estimated using Kaplan-Meier analysis.The 95% CIs were constructed using the z-method and bootstrapping was used to calculate standard errors

Table 35.1.1.9.1
Summary of Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis
ITT Population

	Placebo + BSC N=230	Fruquintinib 5mg + BSC N=461	Difference (Fruquintinib 5mg + BSC) - (Placebo + BSC)
REL			
Mean (95% CI)	4.36 (3.75, 4.96)	3.93 (3.55, 4.32)	-0.43 (-1.15, 0.29)
p-value			>= 0.05

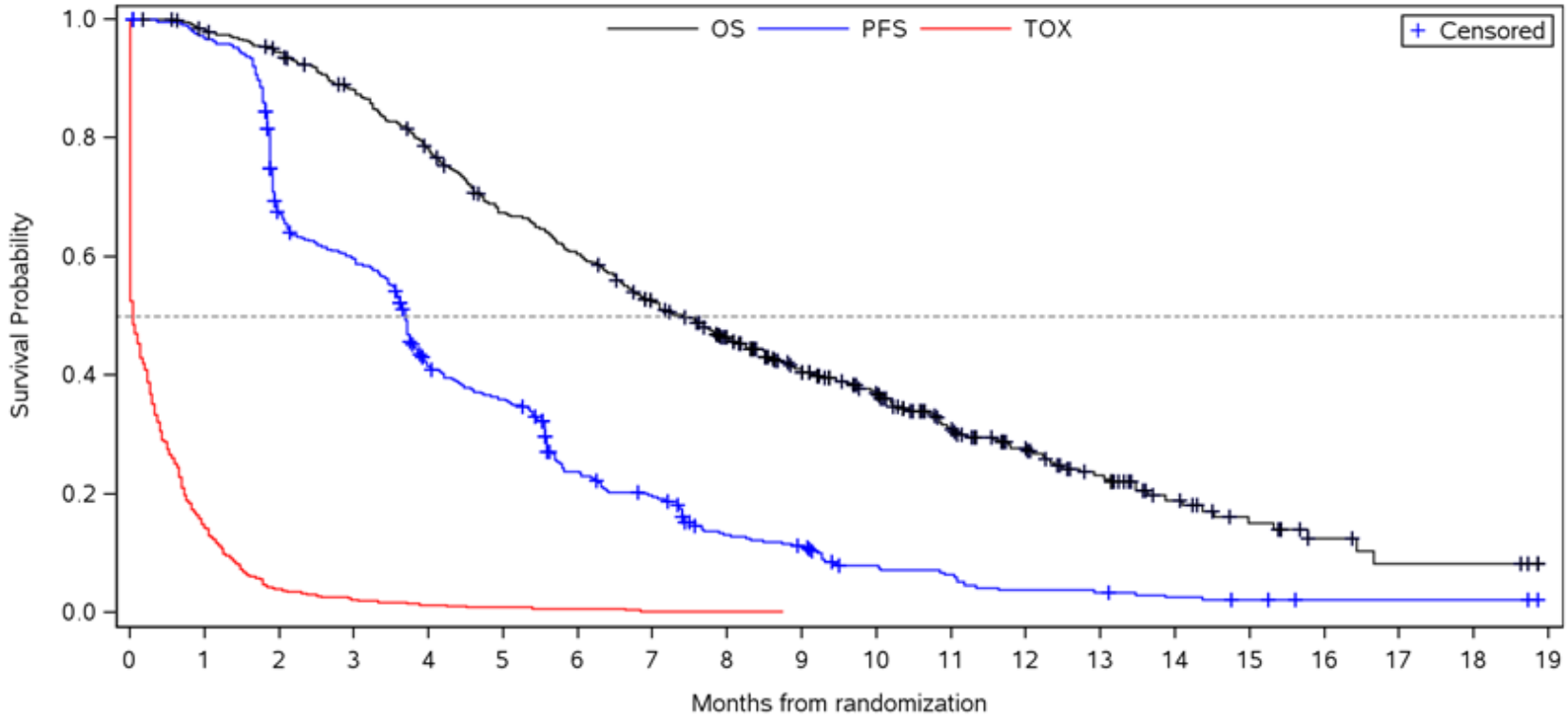
BSC: Best supportive care; Q-TWiST: Quality-adjusted time without symptoms or toxicity; REL: Relapse; TOX: Time of toxicity; TWiST: Time without symptoms or toxicity.
Mean durations of health states were estimated using Kaplan-Meier analysis.The 95% CIs were constructed using the z-method and bootstrapping was used to calculate standard errors

Figure 35.1.1.9.1
Survival Plot of TOX, PFS, OS
Intent-to-Treat Population
Placebo + BSC



Partitioned survival curves for Fruquintinib + BSC and Placebo + BSC.
BSC=Best supportive care; OS=Overall Survival; TOX=Time of Toxicity

Figure 35.1.1.9.1
Survival Plot of TOX, PFS, OS
Intent-to-Treat Population
Fruquintinib + BSC



Partitioned survival curves for Fruquintinib + BSC and Placebo + BSC.
BSC=Best supportive care; OS=Overall Survival; TOX=Time of Toxicity

Table 35.1.1.9.3
Sensitivity analysis of Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST): Serious Adverse Event
ITT Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461	Difference (Fruquintinib + BSC) - (Placebo + BSC)
Duration of health states (months)			
OS			
Mean (95% CI)	6.49 (5.82, 7.17)	8.44 (7.95, 8.93)	1.94 (1.11, 2.78)
PFS			
Mean (95% CI)	2.14 (1.95, 2.32)	4.51 (4.20, 4.82)	2.37 (2.01, 2.73)
Q-TWiST			
Mean (95% CI)	4.26 (3.87, 4.66)	6.41 (6.04, 6.77)	2.14 (1.61, 2.68)
p-value			< 0.05
TWiST			
Mean (95% CI)	2.04 (1.85, 2.22)	4.38 (4.07, 4.68)	2.34 (1.98, 2.70)
p-value			< 0.05
TOX			
Mean (95% CI)	0.10 (0.07, 0.13)	0.13 (0.10, 0.17)	0.03 (-0.02, 0.08)
p-value			>= 0.05
REL			
Mean (95% CI)	4.36 (3.75, 4.96)	3.93 (3.55, 4.32)	-0.43 (-1.15, 0.29)
p-value			>= 0.05

BSC: Best supportive care; Q-TWiST: Quality-adjusted time without symptoms or toxicity; REL: Relapse; TOX: Time of serious toxicity; TWiST: Time without symptoms or toxicity.
Mean durations of health states were estimated using Kaplan-Meier analysis.The 95% CIs were constructed using the z-method and bootstrapping was used to calculate standard errors.

2. Sicherheitspopulation

2.1 Sicherheitsanalysen

2.1.1 UE-Gesamtraten

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	213 (92.6)	451 (98.9)
Number of Subjects Censored, n (%)	17 (7.4)	5 (1.1)
Time to first TEAE (months)		
25% percentile (95% CI)	0.10 (0.07, 0.20)	0.07 (0.07, 0.10)
Median (95% CI)	0.46 (0.39, 0.59)	0.26 (0.23, 0.33)
75% percentile (95% CI)	0.72 (0.69, 0.82)	0.69 (0.66, 0.69)
Min, Max	0.0, 4.6*	0.0, 6.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.410 (0.085)
95% CI		(1.195, 1.664)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	7.7 (4.3, 11.2)	1.8 (0.5, 3.0)
6 months	NE (NE, NE)	0.7 (0.0, 1.6)
9 months	NE (NE, NE)	NE (NE, NE)
12 months	NE (NE, NE)	NE (NE, NE)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	0.46	0.26

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	88 (38.3)	171 (37.5)
Number of Subjects Censored, n (%)	142 (61.7)	285 (62.5)
Time to first TEAE (months)		
25% percentile (95% CI)	1.31 (0.99, 1.94)	2.73 (2.00, 3.25)
Median (95% CI)	NE (4.14, NE)	9.23 (7.75, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.1, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.689 (0.135)
95% CI		(0.529, 0.898)
Log-rank p-value		0.009

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	63.4 (57.0, 69.7)	72.2 (68.0, 76.4)
6 months	52.2 (41.5, 62.8)	59.0 (53.6, 64.3)
9 months	52.2 (41.5, 62.8)	50.6 (43.7, 57.6)
12 months	52.2 (41.5, 62.8)	42.3 (31.5, 53.2)
18 months	NE (NE, NE)	42.3 (31.5, 53.2)
Median Follow-up Time (months)	2.79	3.25

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	200 (87.0)	444 (97.4)
Number of Subjects Censored, n (%)	30 (13.0)	12 (2.6)
Time to first TEAE (months)		
25% percentile (95% CI)	0.10 (0.07, 0.20)	0.07 (0.07, 0.10)
Median (95% CI)	0.54 (0.46, 0.69)	0.30 (0.26, 0.39)
75% percentile (95% CI)	0.76 (0.69, 1.25)	0.69 (NE, NE)
Min, Max	0.0, 4.7*	0.0, 6.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.444 (0.086)
95% CI		(1.219, 1.710)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	11.4 (7.0, 15.7)	2.4 (0.9, 3.9)
6 months	NE (NE, NE)	1.0 (0.0, 2.2)
9 months	NE (NE, NE)	NE (NE, NE)
12 months	NE (NE, NE)	NE (NE, NE)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	0.54	0.30

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	116 (50.4)	286 (62.7)
Number of Subjects Censored, n (%)	114 (49.6)	170 (37.3)
Time to first TEAE (months)		
25% percentile (95% CI)	0.95 (0.72, 1.25)	0.95 (0.69, 1.18)
Median (95% CI)	3.61 (2.27, 4.83)	2.79 (2.53, 3.61)
75% percentile (95% CI)	9.26 (5.36, NE)	8.90 (7.33, NE)
Min, Max	0.1, 9.3	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.090 (0.112)
95% CI		(0.875, 1.357)
Log-rank p-value		0.339

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	54.2 (47.6, 60.7)	48.4 (43.7, 53.0)
6 months	32.1 (19.9, 44.4)	34.3 (29.2, 39.3)
9 months	32.1 (19.9, 44.4)	24.7 (18.5, 31.0)
12 months	0.0 (NE, NE)	18.1 (10.0, 26.3)
18 months	0.0 (NE, NE)	12.1 (1.0, 23.2)
Median Follow-up Time (months)	2.27	2.66

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Discontinuation due to TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	49 (21.3)	93 (20.4)
Number of Subjects Censored, n (%)	181 (78.7)	363 (79.6)
Time to first TEAE (months)		
25% percentile (95% CI)	3.98 (3.15, NE)	7.46 (5.39, 8.90)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.624 (0.184)
95% CI		(0.435, 0.896)
Log-rank p-value		0.013

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Discontinuation due to TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	81.3 (76.2, 86.4)	86.5 (83.4, 89.7)
6 months	65.0 (52.7, 77.4)	78.7 (74.1, 83.2)
9 months	65.0 (52.7, 77.4)	67.6 (60.4, 74.8)
12 months	65.0 (52.7, 77.4)	62.9 (53.6, 72.2)
18 months	NE (NE, NE)	62.9 (53.6, 72.2)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Deaths (Grade 5 TEAEs)

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	45 (19.6)	48 (10.5)
Number of Subjects Censored, n (%)	185 (80.4)	408 (89.5)
Time to first TEAE (months)		
25% percentile (95% CI)	3.98 (2.60, NE)	NE (9.69, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.6, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.344 (0.217)
95% CI		(0.225, 0.527)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.5.1.1A
Summary of Time to Onset of Overall TEAE by ITT
Safety Population
Deaths (Grade 5 TEAEs)

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	80.3 (74.9, 85.7)	93.8 (91.6, 96.1)
6 months	74.8 (66.8, 82.8)	87.4 (83.5, 91.2)
9 months	74.8 (66.8, 82.8)	83.3 (77.7, 88.9)
12 months	74.8 (66.8, 82.8)	81.1 (74.2, 88.0)
18 months	NE (NE, NE)	75.7 (63.6, 87.8)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

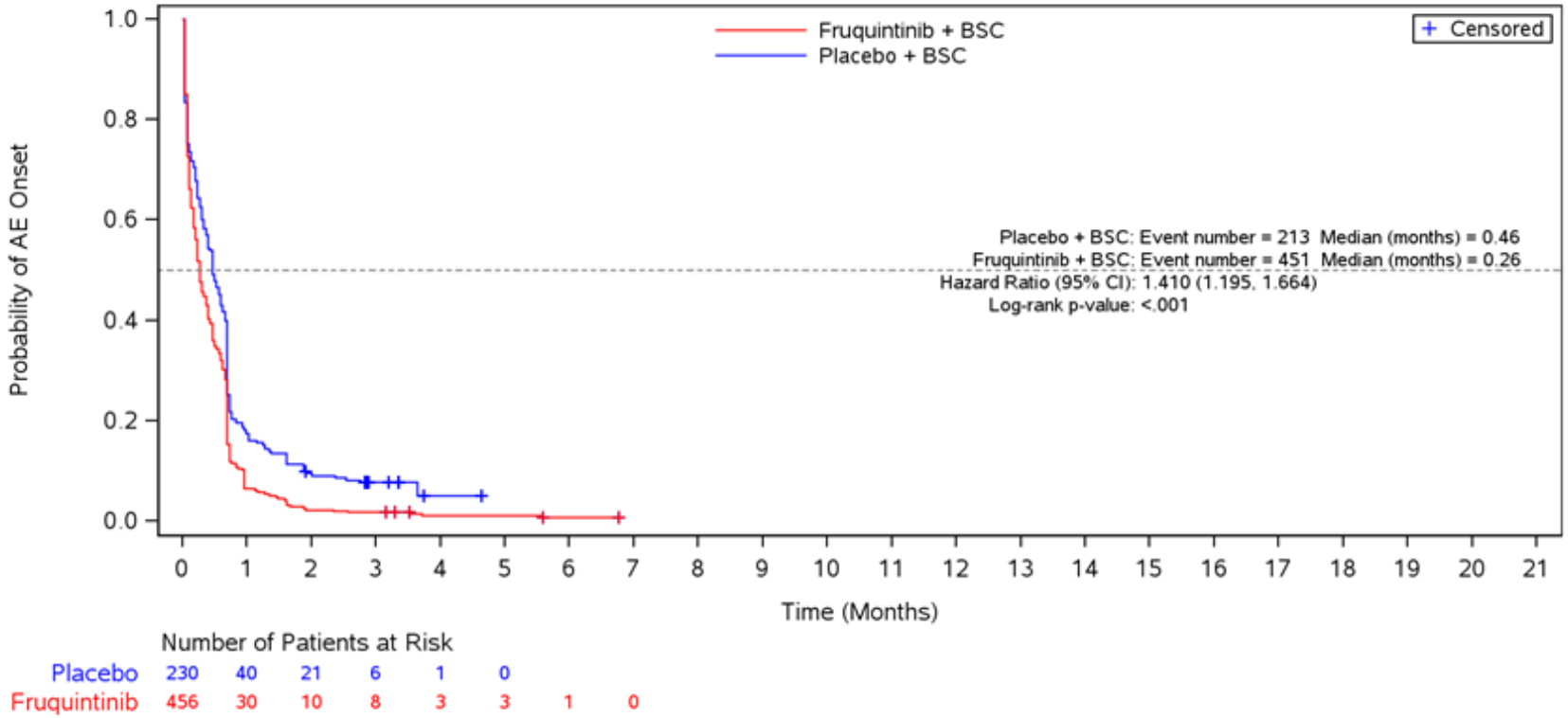
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

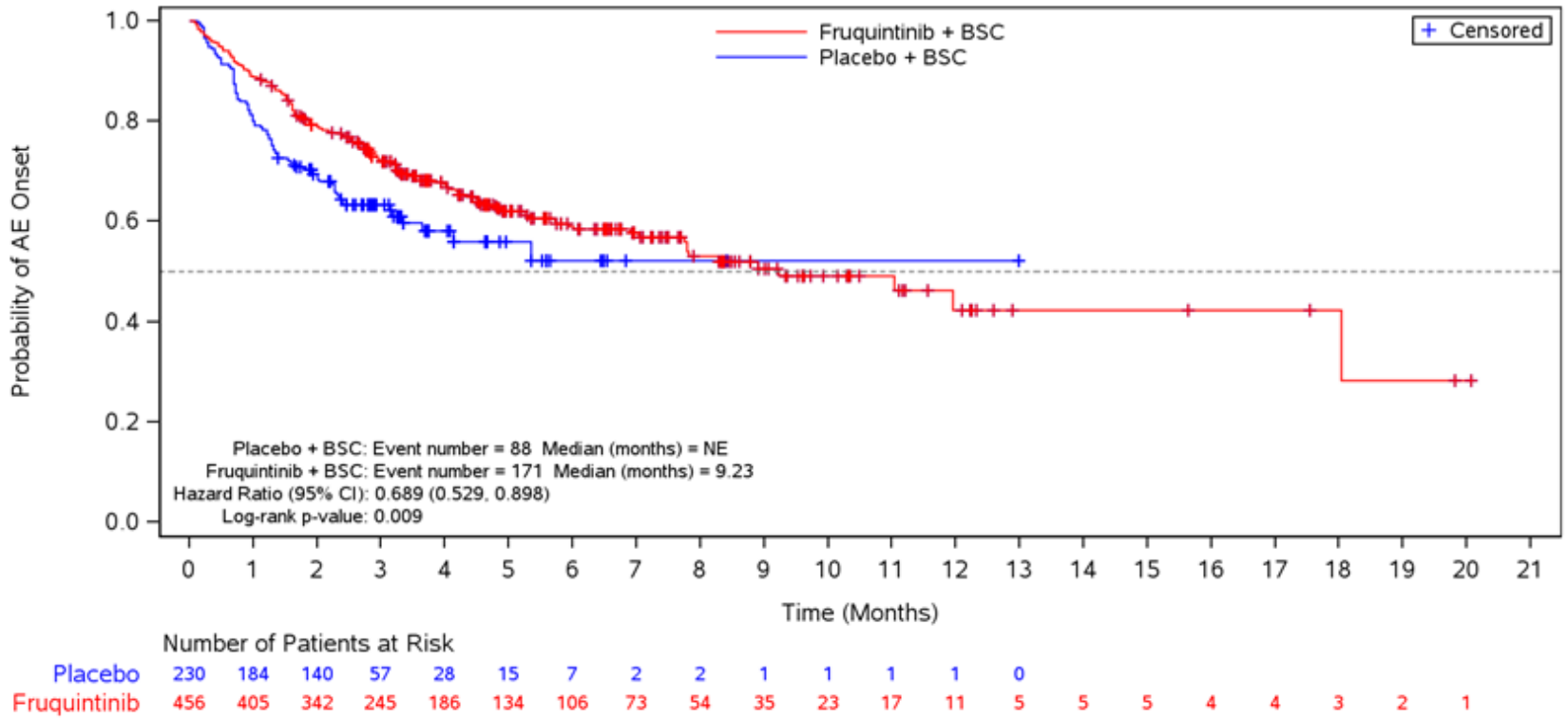
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
TEAE



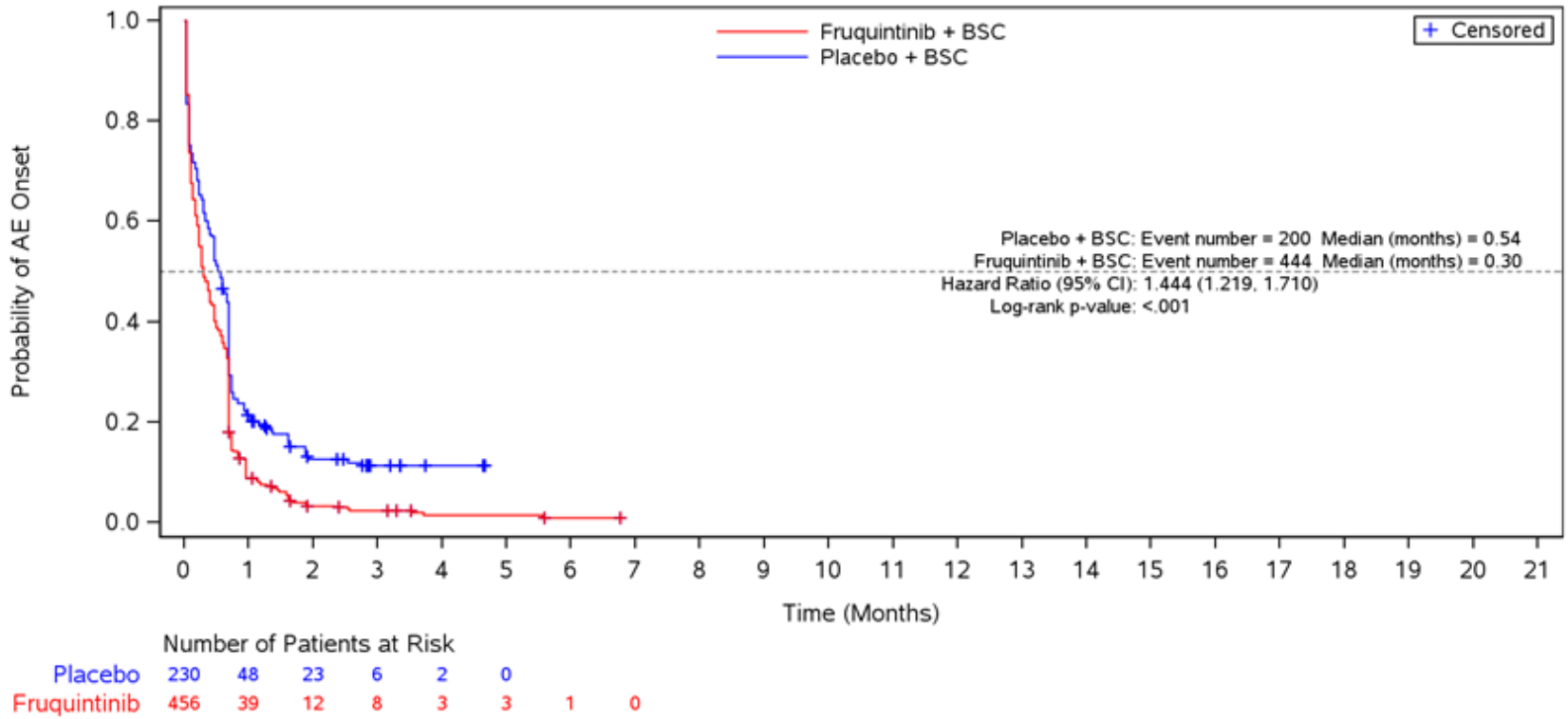
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
Serious TEAE



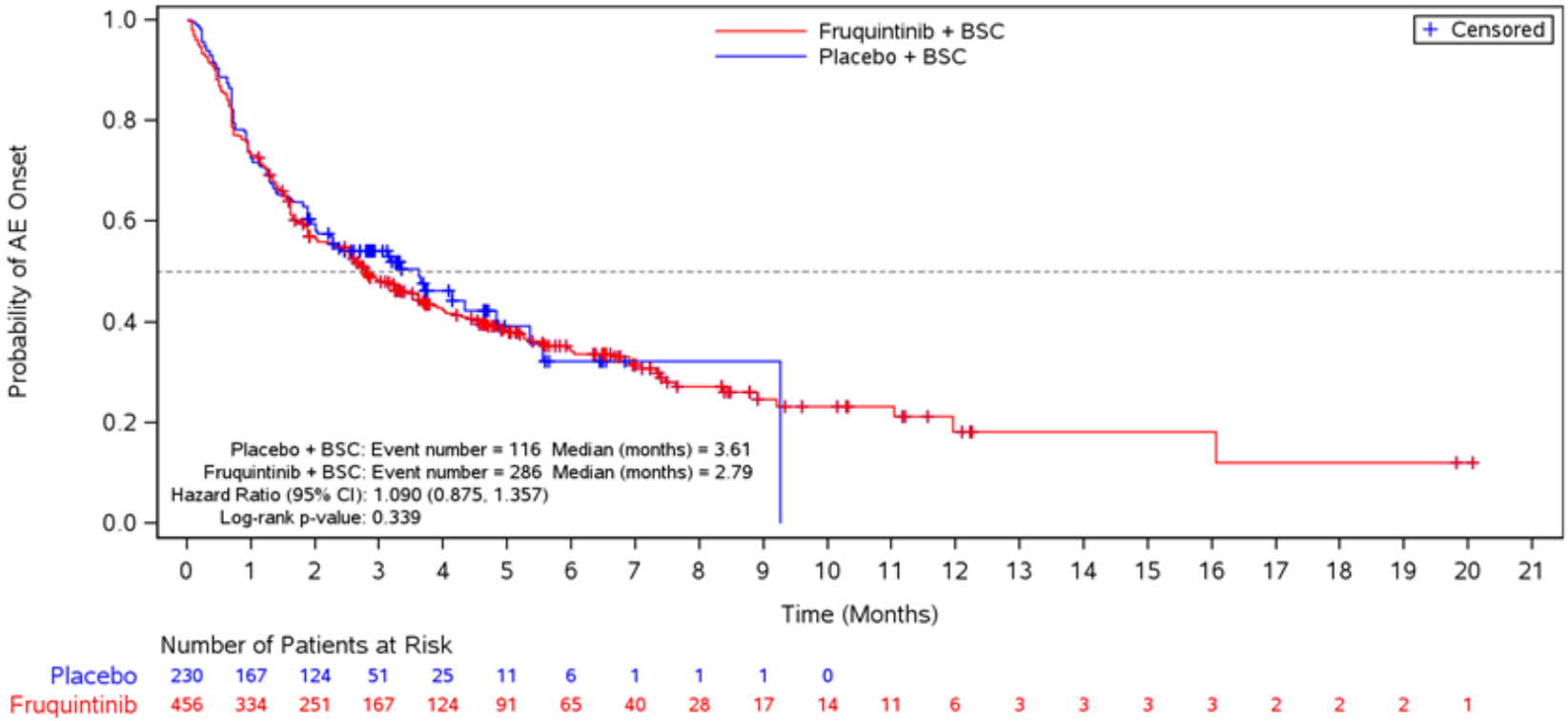
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
TEAE ≤ CTCAE Grade 2



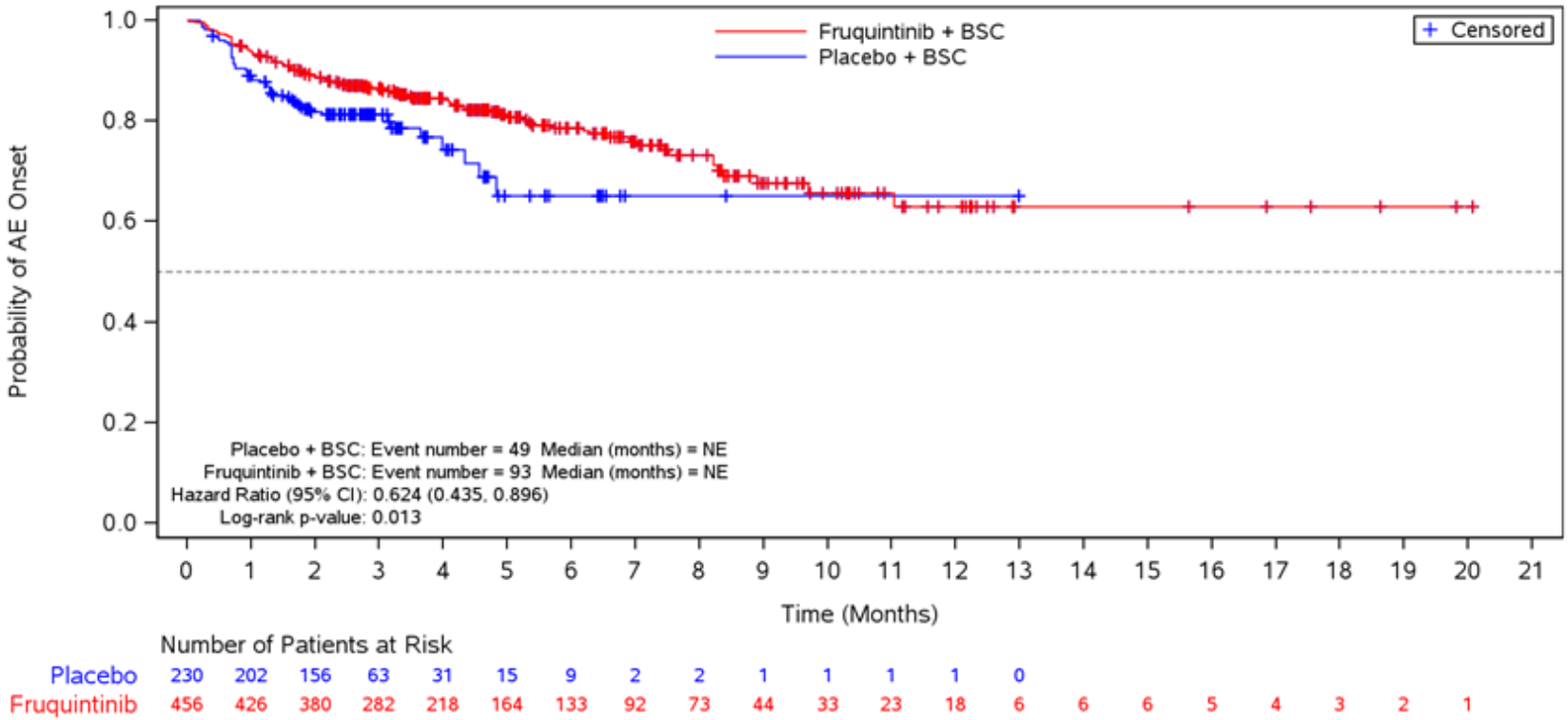
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
TEAE ≥ CTCAE Grade 3



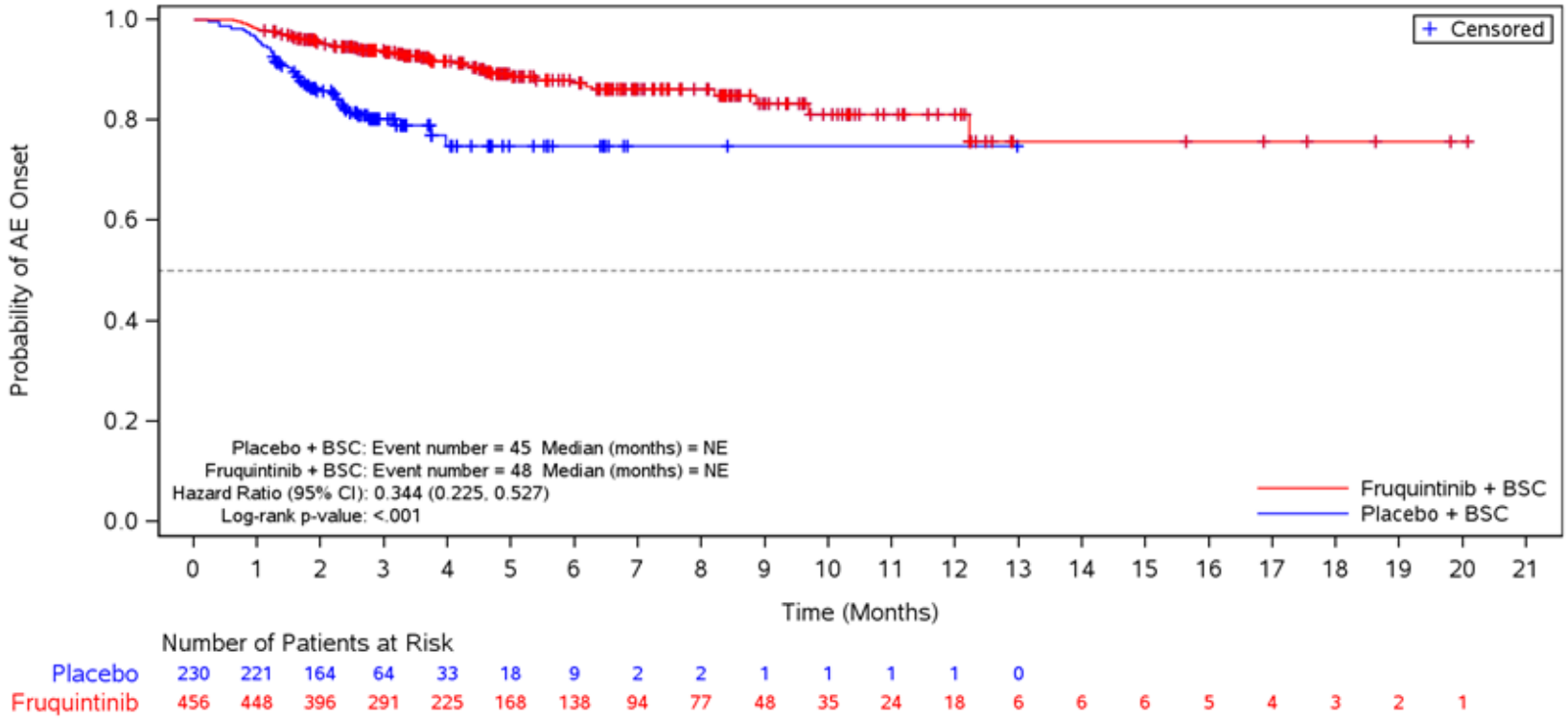
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
Discontinuation due to TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.1.1A
Kaplan-Meier Plot for Time to Onset of Overall TEAE
Safety Population
Deaths (Grade 5 TEAEs)



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

2.1.2 UE-Gesamtraten (ohne erkrankungsbezogene Ereignisse)

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	211 (91.7)	450 (98.7)
Number of Subjects Censored, n (%)	19 (8.3)	6 (1.3)
Time to first TEAE (months)		
25% percentile (95% CI)	0.10 (0.07, 0.20)	0.07 (0.07, 0.10)
Median (95% CI)	0.46 (0.39, 0.59)	0.26 (0.23, 0.33)
75% percentile (95% CI)	0.72 (0.69, 0.82)	0.69 (0.66, 0.69)
Min, Max	0.0, 4.6*	0.0, 6.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.414 (0.085)
95% CI		(1.197, 1.669)
Log-rank p-value		<.001

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	8.3 (4.7, 12.0)	1.9 (0.7, 3.2)
6 months	NE (NE, NE)	0.8 (0.0, 1.8)
9 months	NE (NE, NE)	NE (NE, NE)
12 months	NE (NE, NE)	NE (NE, NE)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	0.46	0.26

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	72 (31.3)	154 (33.8)
Number of Subjects Censored, n (%)	158 (68.7)	302 (66.2)
Time to first TEAE (months)		
25% percentile (95% CI)	1.58 (1.15, 3.15)	2.89 (2.40, 3.61)
Median (95% CI)	NE (5.36, NE)	11.04 (7.82, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.1, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.771 (0.147)
95% CI		(0.578, 1.028)
Log-rank p-value		0.102

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	69.8 (63.7, 75.9)	74.2 (70.1, 78.4)
6 months	58.5 (47.2, 69.9)	63.2 (58.0, 68.4)
9 months	58.5 (47.2, 69.9)	54.3 (47.1, 61.5)
12 months	58.5 (47.2, 69.9)	45.4 (33.8, 56.9)
18 months	NE (NE, NE)	45.4 (33.8, 56.9)
Median Follow-up Time (months)	2.79	3.27

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	200 (87.0)	444 (97.4)
Number of Subjects Censored, n (%)	30 (13.0)	12 (2.6)
Time to first TEAE (months)		
25% percentile (95% CI)	0.10 (0.07, 0.20)	0.07 (0.07, 0.10)
Median (95% CI)	0.54 (0.46, 0.69)	0.30 (0.26, 0.39)
75% percentile (95% CI)	0.76 (0.69, 1.25)	0.69 (NE, NE)
Min, Max	0.0, 4.7*	0.0, 6.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.445 (0.086)
95% CI		(1.220, 1.711)
Log-rank p-value		<.001

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	11.4 (7.0, 15.7)	2.4 (0.9, 3.9)
6 months	NE (NE, NE)	1.0 (0.0, 2.2)
9 months	NE (NE, NE)	NE (NE, NE)
12 months	NE (NE, NE)	NE (NE, NE)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	0.54	0.30

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	103 (44.8)	277 (60.7)
Number of Subjects Censored, n (%)	127 (55.2)	179 (39.3)
Time to first TEAE (months)		
25% percentile (95% CI)	0.99 (0.76, 1.28)	0.95 (0.69, 1.18)
Median (95% CI)	4.14 (3.35, 5.55)	2.86 (2.53, 3.71)
75% percentile (95% CI)	9.26 (5.55, NE)	9.20 (7.39, NE)
Min, Max	0.1, 9.3	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.202 (0.117)
95% CI		(0.955, 1.512)
Log-rank p-value		0.078

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	59.2 (52.7, 65.6)	49.2 (44.5, 53.8)
6 months	35.9 (22.4, 49.3)	36.2 (31.0, 41.4)
9 months	35.9 (22.4, 49.3)	26.1 (19.6, 32.6)
12 months	0.0 (NE, NE)	19.2 (10.5, 27.8)
18 months	0.0 (NE, NE)	12.8 (1.0, 24.5)
Median Follow-up Time (months)	2.35	2.66

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Discontinuation due to TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	40 (17.4)	85 (18.6)
Number of Subjects Censored, n (%)	190 (82.6)	371 (81.4)
Time to first TEAE (months)		
25% percentile (95% CI)	4.57 (3.65, NE)	8.21 (6.18, 11.04)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.698 (0.200)
95% CI		(0.472, 1.033)
Log-rank p-value		0.083

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Discontinuation due to TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	84.6 (79.8, 89.4)	87.6 (84.6, 90.7)
6 months	68.9 (56.1, 81.6)	80.5 (76.2, 84.9)
9 months	68.9 (56.1, 81.6)	69.9 (62.7, 77.0)
12 months	68.9 (56.1, 81.6)	65.0 (55.5, 74.4)
18 months	NE (NE, NE)	65.0 (55.5, 74.4)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Deaths (Grade 5 TEAEs)

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	16 (7.0)	19 (4.2)
Number of Subjects Censored, n (%)	214 (93.0)	437 (95.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.360 (0.359)
95% CI		(0.178, 0.727)
Log-rank p-value		0.003

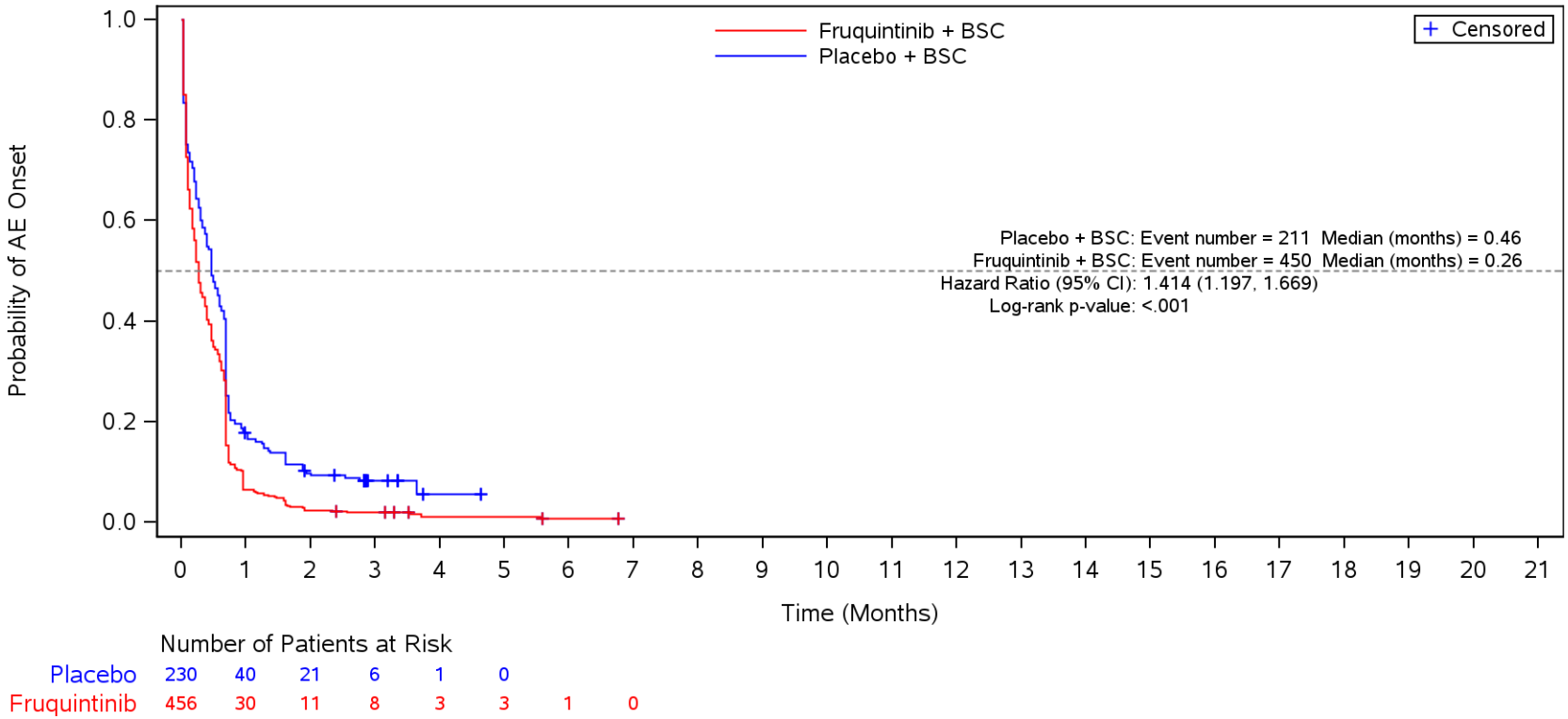
* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Table 35.1.1.5.2.3A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Deaths (Grade 5 TEAEs)

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	92.4 (88.7, 96.1)	97.7 (96.3, 99.1)
6 months	89.7 (83.3, 96.1)	95.5 (93.1, 97.9)
9 months	89.7 (83.3, 96.1)	92.8 (88.9, 96.7)
12 months	89.7 (83.3, 96.1)	90.4 (84.3, 96.4)
18 months	NE (NE, NE)	90.4 (84.3, 96.4)
Median Follow-up Time (months)	2.83	3.94

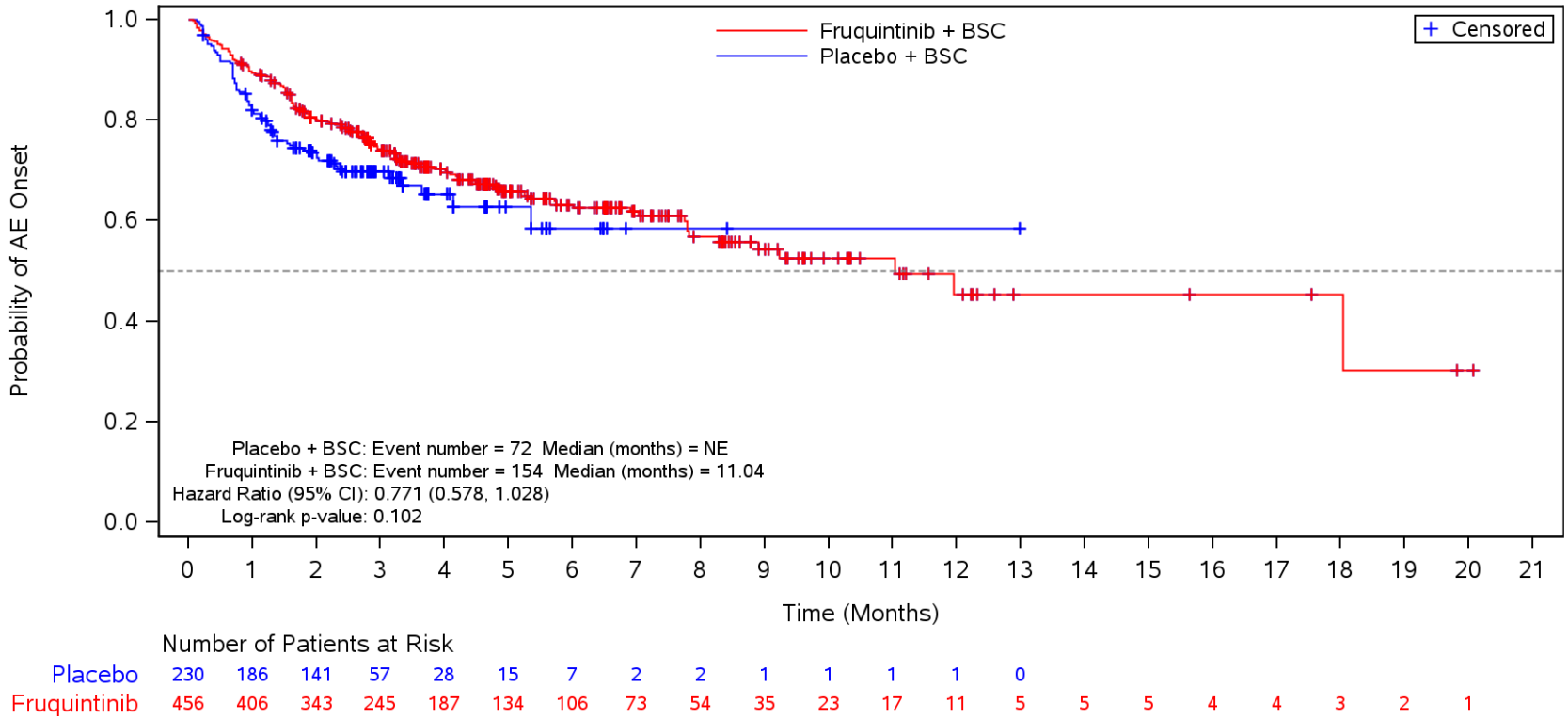
* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.
Disease-related AE(PT) are: Disease progression, Malignant neoplasm progression, Neoplasm progression, Colorectal cancer metastatic, Tumor pain, Tumor invasion, Metastasis, Metastases to meninges, Metastases to liver, Metastases to central nervous system, Cancer pain, Lung cancer metastatic.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE



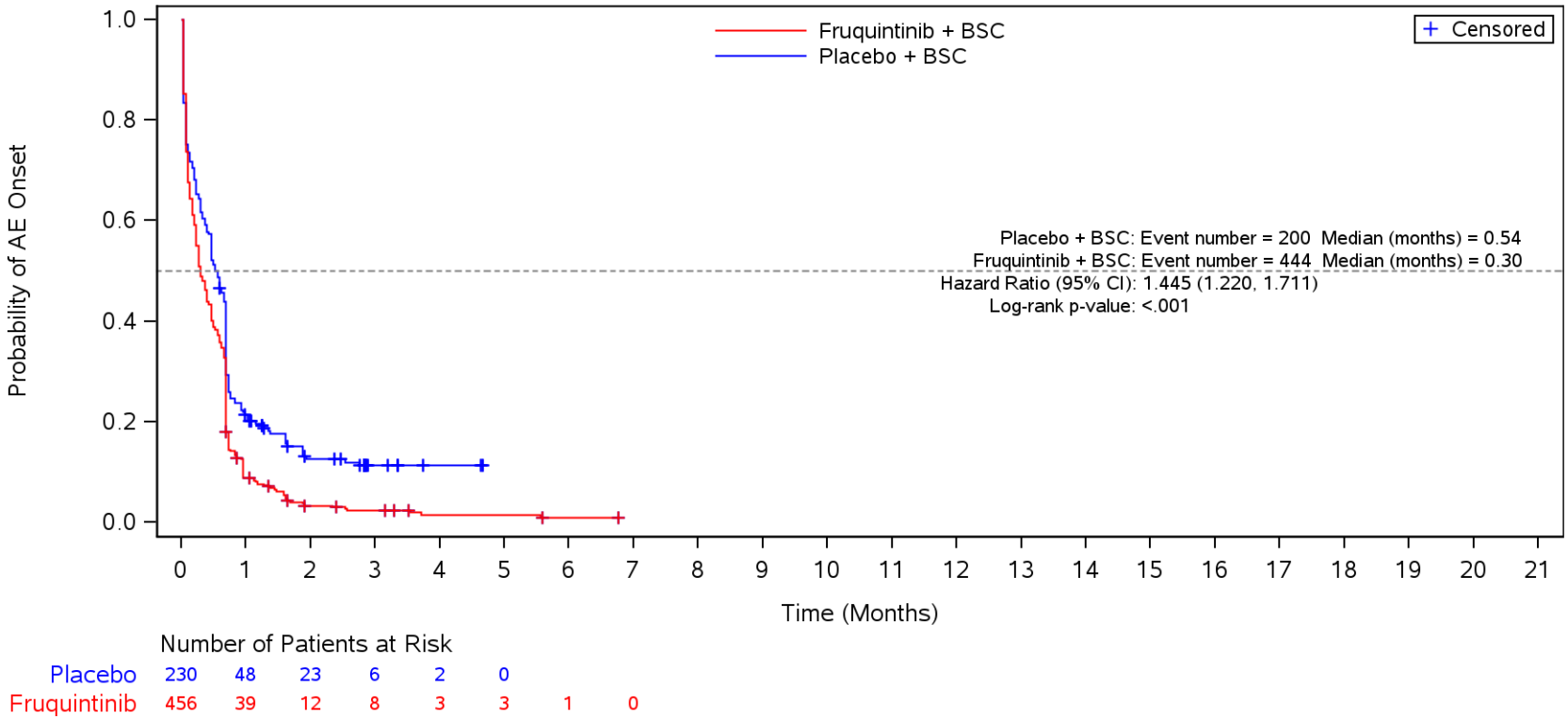
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE



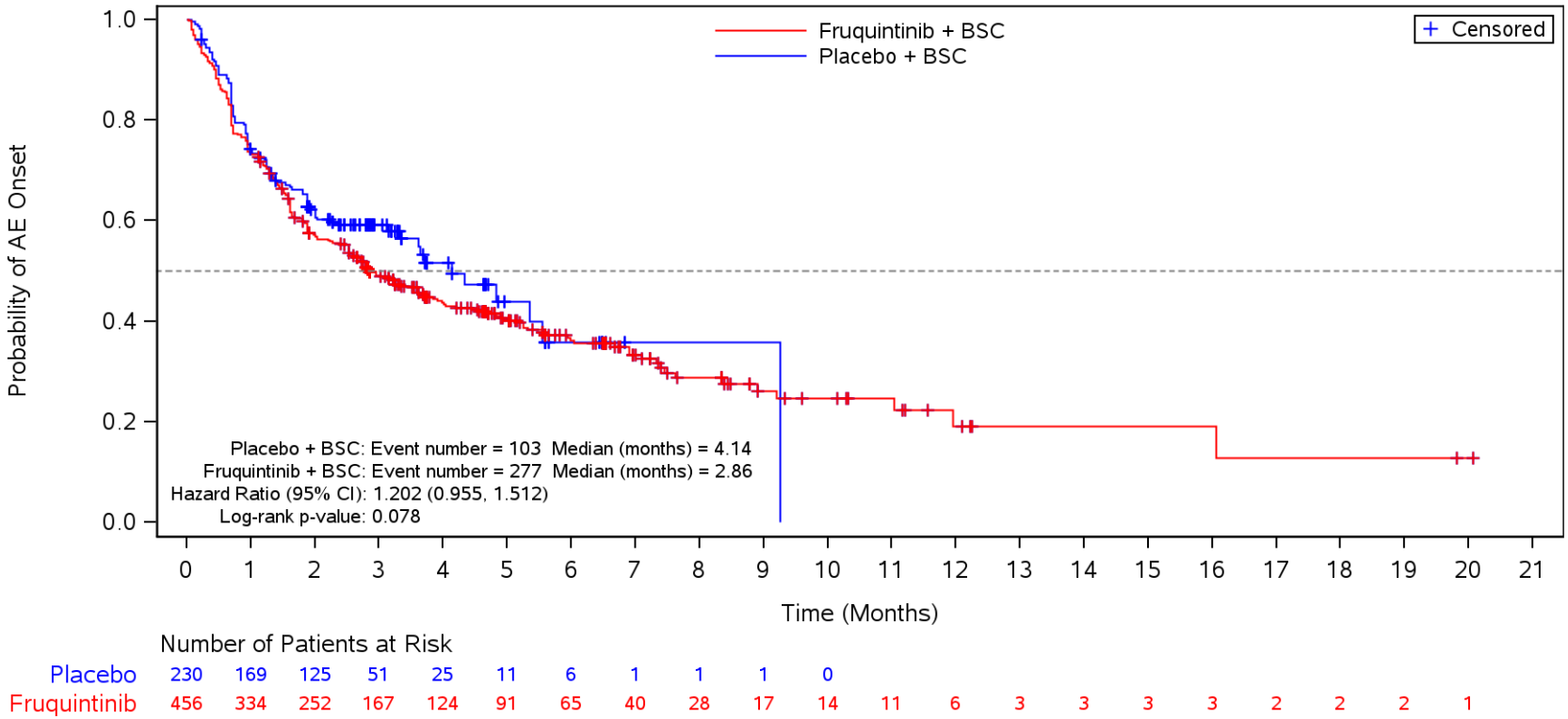
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≤ CTCAE Grade 2



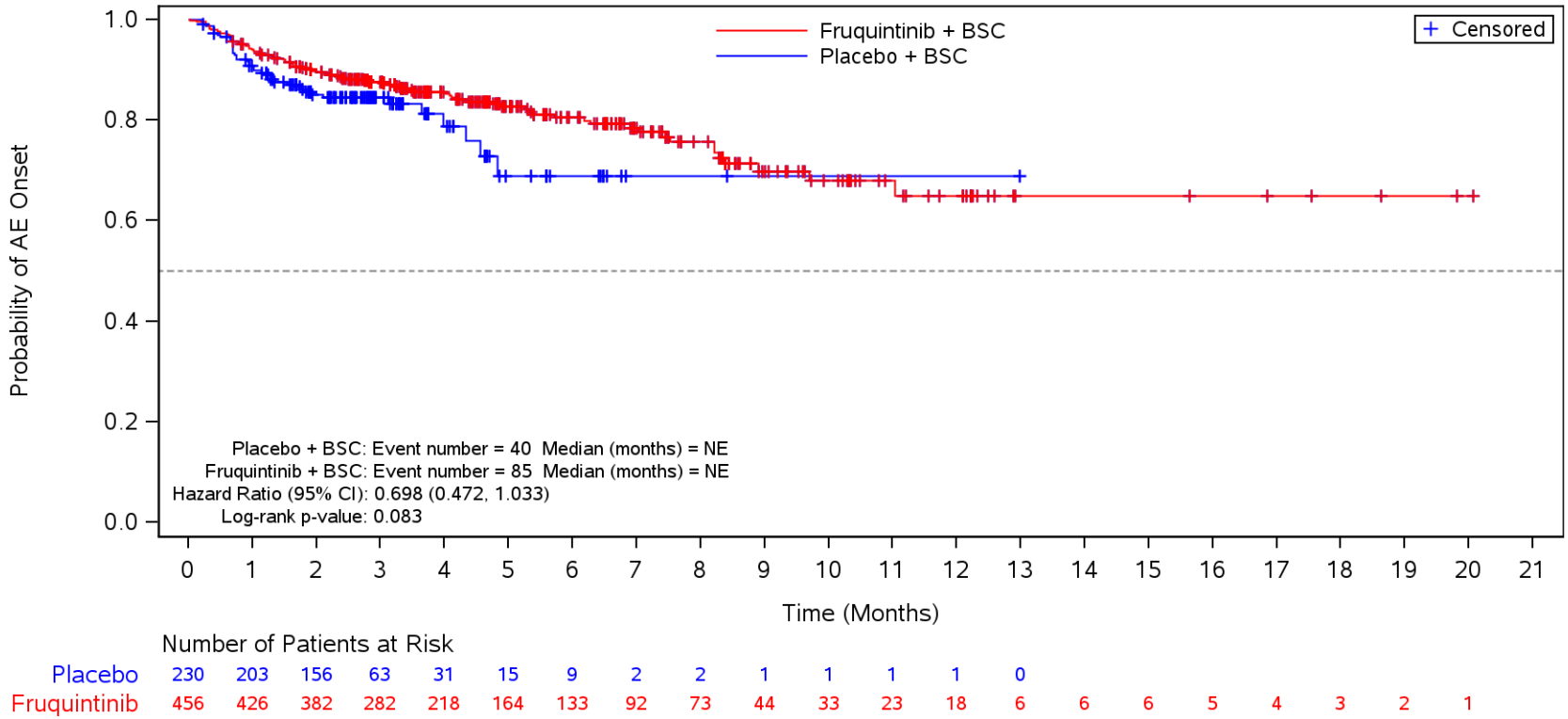
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≥ CTCAE Grade 3



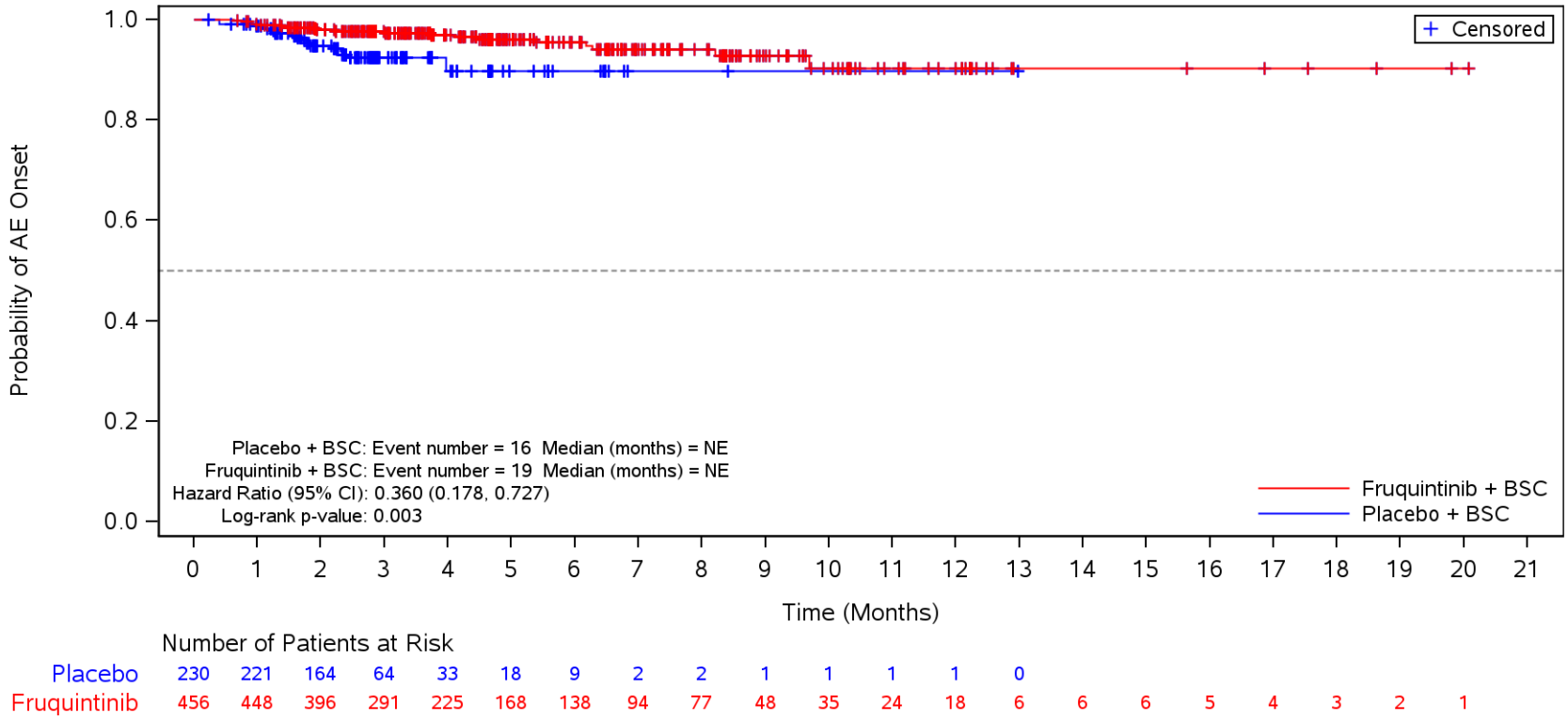
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Discontinuation due to TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.3A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Deaths (Grade 5 TEAEs)



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	211 (91.7)	450 (98.7)
Number of Subjects Censored, n (%)	19 (8.3)	6 (1.3)
Time to first TEAE (months)		
25% percentile (95% CI)	0.10 (0.07, 0.20)	0.07 (0.07, 0.10)
Median (95% CI)	0.46 (0.39, 0.59)	0.26 (0.23, 0.33)
75% percentile (95% CI)	0.72 (0.69, 0.82)	0.69 (0.66, 0.69)
Min, Max	0.0, 4.6*	0.0, 6.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.414 (0.085)
95% CI		(1.197, 1.669)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Disease-related AE(PT) is: Disease progression.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	8.3 (4.7, 12.0)	1.8 (0.5, 3.0)
6 months	NE (NE, NE)	0.7 (0.0, 1.6)
9 months	NE (NE, NE)	NE (NE, NE)
12 months	NE (NE, NE)	NE (NE, NE)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	0.46	0.26

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Disease-related AE(PT) is: Disease progression.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	75 (32.6)	159 (34.9)
Number of Subjects Censored, n (%)	155 (67.4)	297 (65.1)
Time to first TEAE (months)		
25% percentile (95% CI)	1.54 (1.02, 2.33)	2.86 (2.20, 3.48)
Median (95% CI)	NE (5.36, NE)	11.04 (7.82, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.1, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.760 (0.144)
95% CI		(0.573, 1.008)
Log-rank p-value		0.076

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Disease-related AE(PT) is: Disease progression.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	68.6 (62.4, 74.7)	73.8 (69.7, 77.9)
6 months	57.5 (46.3, 68.8)	61.8 (56.6, 67.1)
9 months	57.5 (46.3, 68.8)	53.1 (46.0, 60.2)
12 months	57.5 (46.3, 68.8)	44.4 (33.1, 55.7)
18 months	NE (NE, NE)	44.4 (33.1, 55.7)
Median Follow-up Time (months)	2.79	3.25

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Disease-related AE(PT) is: Disease progression.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	105 (45.7)	279 (61.2)
Number of Subjects Censored, n (%)	125 (54.3)	177 (38.8)
Time to first TEAE (months)		
25% percentile (95% CI)	0.95 (0.72, 1.28)	0.95 (0.69, 1.18)
Median (95% CI)	4.14 (3.35, 5.55)	2.86 (2.53, 3.61)
75% percentile (95% CI)	9.26 (5.55, NE)	9.20 (7.39, NE)
Min, Max	0.1, 9.3	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.184 (0.116)
95% CI		(0.943, 1.488)
Log-rank p-value		0.099

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Disease-related AE(PT) is: Disease progression.

Table 35.1.1.5.2.2A
Summary of Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	58.5 (52.0, 64.9)	49.0 (44.3, 53.6)
6 months	35.5 (22.2, 48.8)	35.8 (30.7, 41.0)
9 months	35.5 (22.2, 48.8)	25.9 (19.4, 32.3)
12 months	0.0 (NE, NE)	19.0 (10.4, 27.5)
18 months	0.0 (NE, NE)	12.6 (1.0, 24.3)
Median Follow-up Time (months)	2.30	2.66

* indicates censored value.

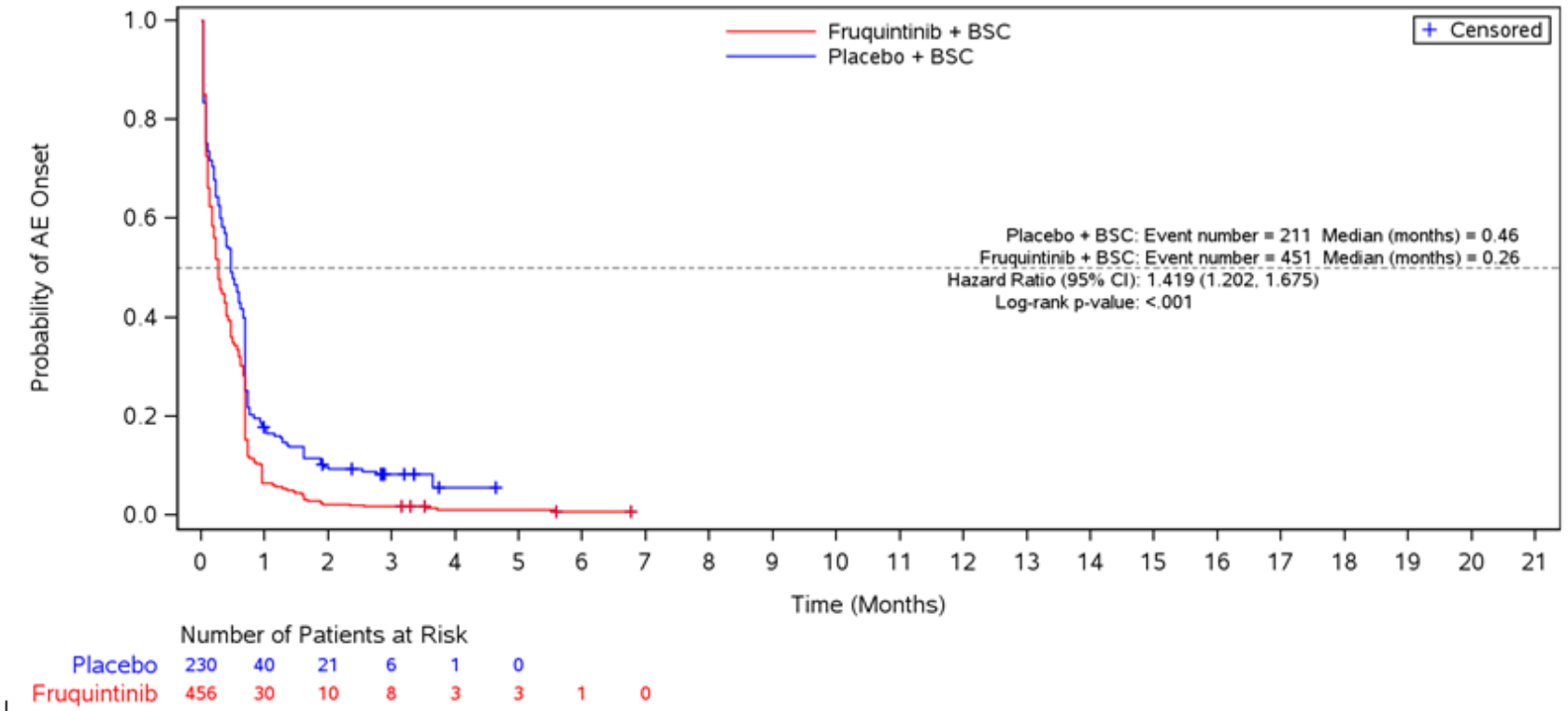
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

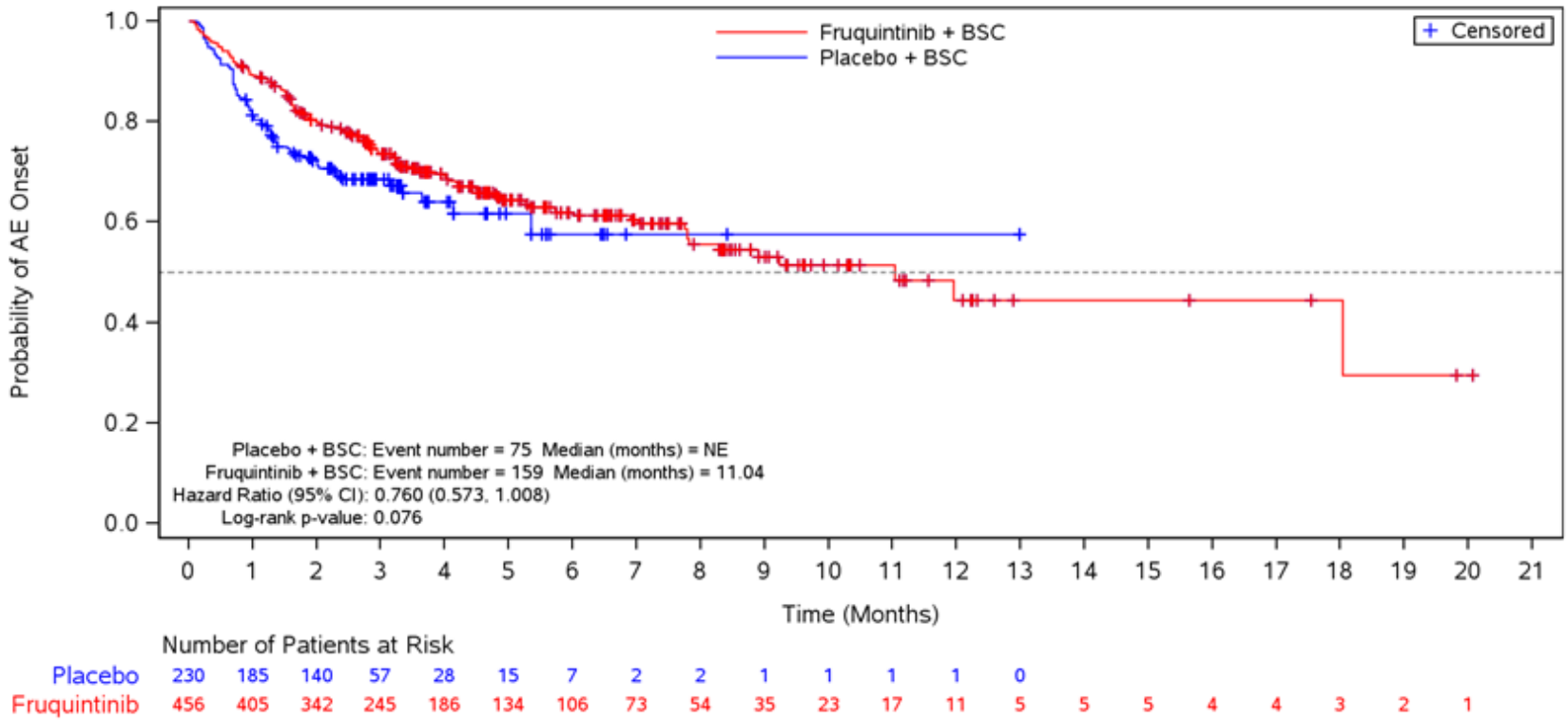
Disease-related AE(PT) is: Disease progression.

Figure 35.1.1.5.2.2A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.5.2.2A
Kaplan-Meier Plot for Time to Onset of Overall TEAE Excluding Disease Related Events
Safety Population
Serious TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

2.1.3 UE auf SOC-/PT-Level

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	129 (56.1)	315 (69.1)
Number of Subjects Censored, n (%)	101 (43.9)	141 (30.9)
Time to first TEAE (months)		
25% percentile (95% CI)	0.69 (0.49, 0.72)	0.43 (0.30, 0.62)
Median (95% CI)	1.87 (1.35, 3.19)	1.25 (0.95, 1.61)
75% percentile (95% CI)	NE (NE, NE)	6.93 (4.60, NE)
Min, Max	0.0, 13.0*	0.0, 12.5*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.245 (0.105)
95% CI		(1.013, 1.531)
Log-rank p-value		0.054

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	43.6 (36.9, 50.3)	37.8 (33.3, 42.3)
6 months	35.3 (25.3, 45.4)	25.9 (21.1, 30.7)
9 months	35.3 (25.3, 45.4)	20.8 (15.2, 26.4)
12 months	35.3 (25.3, 45.4)	20.8 (15.2, 26.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.63	1.15

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	52 (22.6)	155 (34.0)
Number of Subjects Censored, n (%)	178 (77.4)	301 (66.0)
Time to first TEAE (months)		
25% percentile (95% CI)	4.70 (1.61, NE)	1.35 (0.92, 1.74)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 16.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.437 (0.161)
95% CI		(1.048, 1.970)
Log-rank p-value		0.024

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	77.0 (71.3, 82.7)	67.7 (63.3, 72.1)
6 months	70.8 (60.4, 81.2)	63.8 (59.0, 68.6)
9 months	70.8 (60.4, 81.2)	61.2 (55.3, 67.2)
12 months	70.8 (60.4, 81.2)	61.2 (55.3, 67.2)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.55	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Fatigue**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	37 (16.1)	91 (20.0)
Number of Subjects Censored, n (%)	193 (83.9)	365 (80.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (4.60, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.140 (0.197)
95% CI		(0.775, 1.676)
Log-rank p-value		0.547

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Fatigue**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	82.7 (77.6, 87.9)	81.5 (77.8, 85.1)
6 months	82.7 (77.6, 87.9)	78.4 (74.2, 82.6)
9 months	82.7 (77.6, 87.9)	76.3 (71.4, 81.3)
12 months	82.7 (77.6, 87.9)	76.3 (71.4, 81.3)
18 months	NE (NE, NE)	76.3 (71.4, 81.3)
Median Follow-up Time (months)	2.60	3.15

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Pyrexia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	23 (10.0)	46 (10.1)
Number of Subjects Censored, n (%)	207 (90.0)	410 (89.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (4.70, NE)	NE (11.53, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.840 (0.261)
95% CI		(0.504, 1.400)
Log-rank p-value		0.454

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Pyrexia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	89.4 (85.1, 93.6)	91.6 (89.0, 94.2)
6 months	84.6 (74.8, 94.5)	89.0 (85.7, 92.3)
9 months	84.6 (74.8, 94.5)	87.5 (83.7, 91.3)
12 months	84.6 (74.8, 94.5)	82.9 (73.4, 92.4)
18 months	NE (NE, NE)	82.9 (73.4, 92.4)
Median Follow-up Time (months)	2.79	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Mucosal inflammation**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	6 (2.6)	62 (13.6)
Number of Subjects Censored, n (%)	224 (97.4)	394 (86.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.24 (13.24, NE)
Median (95% CI)	NE (NE, NE)	NE (13.24, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.24, NE)
Min, Max	0.1, 13.0*	0.1, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.909 (0.429)
95% CI		(2.117, 11.381)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Mucosal inflammation**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.2 (95.0, 99.4)	87.7 (84.6, 90.7)
6 months	97.2 (95.0, 99.4)	86.0 (82.6, 89.4)
9 months	97.2 (95.0, 99.4)	83.8 (79.3, 88.3)
12 months	97.2 (95.0, 99.4)	83.8 (79.3, 88.3)
18 months	NE (NE, NE)	55.9 (11.1, 100.0)
Median Follow-up Time (months)	2.83	3.50

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	28 (12.2)	27 (5.9)
Number of Subjects Censored, n (%)	202 (87.8)	429 (94.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (12.22, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.338 (0.278)
95% CI		(0.196, 0.583)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	87.2 (82.5, 91.9)	96.0 (94.2, 97.9)
6 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
9 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
12 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
18 months	NE (NE, NE)	85.9 (73.9, 97.9)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Oedema peripheral**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	17 (7.4)	22 (4.8)
Number of Subjects Censored, n (%)	213 (92.6)	434 (95.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.557 (0.329)
95% CI		(0.292, 1.062)
Log-rank p-value		0.069

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Oedema peripheral**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	92.1 (88.5, 95.8)	95.4 (93.4, 97.4)
6 months	92.1 (88.5, 95.8)	95.4 (93.4, 97.4)
9 months	92.1 (88.5, 95.8)	93.4 (89.1, 97.7)
12 months	92.1 (88.5, 95.8)	90.6 (83.7, 97.5)
18 months	NE (NE, NE)	90.6 (83.7, 97.5)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **General physical health deterioration**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	16 (3.5)
Number of Subjects Censored, n (%)	225 (97.8)	440 (96.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.932 (0.538)
95% CI		(0.325, 2.674)
Log-rank p-value		0.824

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **General physical health deterioration**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.6 (95.6, 99.7)	98.2 (96.9, 99.4)
6 months	97.6 (95.6, 99.7)	96.5 (94.4, 98.6)
9 months	97.6 (95.6, 99.7)	95.2 (92.0, 98.4)
12 months	97.6 (95.6, 99.7)	88.0 (79.5, 96.4)
18 months	NE (NE, NE)	88.0 (79.5, 96.4)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Condition aggravated**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	11 (2.4)
Number of Subjects Censored, n (%)	226 (98.3)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.957 (0.598)
95% CI		(0.297, 3.089)
Log-rank p-value		0.890

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Condition aggravated**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.8 (95.5, 100.0)	98.0 (96.7, 99.4)
6 months	97.8 (95.5, 100.0)	97.1 (95.3, 99.0)
9 months	97.8 (95.5, 100.0)	95.9 (92.8, 98.9)
12 months	97.8 (95.5, 100.0)	95.9 (92.8, 98.9)
18 months	NE (NE, NE)	95.9 (92.8, 98.9)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Chills**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	11 (2.4)
Number of Subjects Censored, n (%)	228 (99.1)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.208 (0.783)
95% CI		(0.476, 10.240)
Log-rank p-value		0.280

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Chills**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	98.2 (97.0, 99.4)
6 months	99.1 (97.9, 100.0)	97.1 (95.1, 99.1)
9 months	99.1 (97.9, 100.0)	95.3 (91.3, 99.3)
12 months	99.1 (97.9, 100.0)	95.3 (91.3, 99.3)
18 months	NE (NE, NE)	95.3 (91.3, 99.3)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	131 (57.0)	309 (67.8)
Number of Subjects Censored, n (%)	99 (43.0)	147 (32.2)
Time to first TEAE (months)		
25% percentile (95% CI)	0.56 (0.39, 0.69)	0.49 (0.46, 0.69)
Median (95% CI)	1.61 (1.31, 2.27)	1.51 (1.02, 1.87)
75% percentile (95% CI)	5.59 (4.34, NE)	6.47 (4.90, 10.12)
Min, Max	0.0, 6.4*	0.0, 16.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.065 (0.106)
95% CI		(0.865, 1.310)
Log-rank p-value		0.515

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	41.1 (34.0, 48.2)	38.7 (34.1, 43.3)
6 months	20.2 (4.6, 35.8)	25.3 (20.1, 30.5)
9 months	NE (NE, NE)	19.1 (13.2, 25.0)
12 months	NE (NE, NE)	16.4 (9.3, 23.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	1.38	1.36

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Diarrhoea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	24 (10.4)	110 (24.1)
Number of Subjects Censored, n (%)	206 (89.6)	346 (75.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	5.55 (3.02, 7.33)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.047 (0.227)
95% CI		(1.311, 3.196)
Log-rank p-value		0.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Diarrhoea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	89.2 (85.1, 93.3)	79.2 (75.3, 83.0)
6 months	89.2 (85.1, 93.3)	72.2 (67.1, 77.4)
9 months	89.2 (85.1, 93.3)	68.5 (62.5, 74.6)
12 months	89.2 (85.1, 93.3)	63.3 (51.9, 74.7)
18 months	NE (NE, NE)	63.3 (51.9, 74.7)
Median Follow-up Time (months)	2.71	2.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Nausea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	42 (18.3)	79 (17.3)
Number of Subjects Censored, n (%)	188 (81.7)	377 (82.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (4.34, NE)	9.00 (5.68, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.710 (0.196)
95% CI		(0.484, 1.043)
Log-rank p-value		0.082

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Nausea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	81.3 (76.1, 86.5)	85.2 (81.8, 88.6)
6 months	77.9 (69.7, 86.1)	79.7 (75.1, 84.3)
9 months	77.9 (69.7, 86.1)	76.9 (71.4, 82.3)
12 months	77.9 (69.7, 86.1)	73.0 (65.7, 80.4)
18 months	NE (NE, NE)	73.0 (65.7, 80.4)
Median Follow-up Time (months)	2.61	3.38

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	37 (16.1)	83 (18.2)
Number of Subjects Censored, n (%)	193 (83.9)	373 (81.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (4.57, NE)	9.23 (6.18, NE)
Median (95% CI)	NE (NE, NE)	NE (12.25, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.853 (0.202)
95% CI		(0.573, 1.268)
Log-rank p-value		0.500

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	82.2 (76.6, 87.8)	84.9 (81.5, 88.4)
6 months	79.1 (70.9, 87.2)	80.0 (75.6, 84.3)
9 months	79.1 (70.9, 87.2)	75.3 (69.5, 81.1)
12 months	79.1 (70.9, 87.2)	70.5 (62.0, 79.0)
18 months	NE (NE, NE)	62.7 (46.3, 79.0)
Median Follow-up Time (months)	2.79	3.35

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Constipation**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	22 (9.6)	78 (17.1)
Number of Subjects Censored, n (%)	208 (90.4)	378 (82.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	9.33 (5.82, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.384 (0.245)
95% CI		(0.856, 2.238)
Log-rank p-value		0.196

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Constipation**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	89.3 (84.5, 94.1)	85.3 (81.9, 88.7)
6 months	87.7 (82.1, 93.3)	79.8 (75.3, 84.3)
9 months	87.7 (82.1, 93.3)	76.8 (71.3, 82.2)
12 months	87.7 (82.1, 93.3)	74.6 (67.9, 81.3)
18 months	NE (NE, NE)	74.6 (67.9, 81.3)
Median Follow-up Time (months)	2.79	3.35

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Vomiting**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	28 (12.2)	66 (14.5)
Number of Subjects Censored, n (%)	202 (87.8)	390 (85.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.36, NE)	18.04 (7.39, NE)
Median (95% CI)	NE (NE, NE)	NE (18.04, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.1, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.877 (0.232)
95% CI		(0.557, 1.382)
Log-rank p-value		0.610

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Vomiting**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	87.8 (83.4, 92.2)	88.9 (86.0, 91.9)
6 months	81.0 (70.4, 91.6)	83.7 (79.5, 87.9)
9 months	81.0 (70.4, 91.6)	80.1 (74.8, 85.4)
12 months	81.0 (70.4, 91.6)	75.5 (67.6, 83.5)
18 months	NE (NE, NE)	75.5 (67.6, 83.5)
Median Follow-up Time (months)	2.79	3.68

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Stomatitis**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	8 (3.5)	67 (14.7)
Number of Subjects Censored, n (%)	222 (96.5)	389 (85.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.088 (0.375)
95% CI		(1.959, 8.532)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Stomatitis**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	96.2 (93.6, 98.8)	86.6 (83.4, 89.7)
6 months	96.2 (93.6, 98.8)	84.3 (80.7, 88.0)
9 months	96.2 (93.6, 98.8)	82.1 (77.5, 86.8)
12 months	96.2 (93.6, 98.8)	82.1 (77.5, 86.8)
18 months	NE (NE, NE)	82.1 (77.5, 86.8)
Median Follow-up Time (months)	2.83	3.40

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain upper**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	8 (3.5)	34 (7.5)
Number of Subjects Censored, n (%)	222 (96.5)	422 (92.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.59, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.736 (0.398)
95% CI		(0.795, 3.789)
Log-rank p-value		0.182

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain upper**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	96.8 (94.5, 99.1)	93.8 (91.5, 96.1)
6 months	90.7 (79.1, 100.0)	91.0 (87.9, 94.2)
9 months	NE (NE, NE)	89.7 (85.7, 93.7)
12 months	NE (NE, NE)	89.7 (85.7, 93.7)
18 months	NE (NE, NE)	89.7 (85.7, 93.7)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Proctalgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	16 (3.5)
Number of Subjects Censored, n (%)	226 (98.3)	440 (96.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.705 (0.567)
95% CI		(0.561, 5.183)
Log-rank p-value		0.331

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Proctalgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.1 (96.3, 99.9)	97.1 (95.6, 98.7)
6 months	98.1 (96.3, 99.9)	96.0 (93.8, 98.2)
9 months	98.1 (96.3, 99.9)	94.8 (91.6, 98.0)
12 months	98.1 (96.3, 99.9)	94.8 (91.6, 98.0)
18 months	NE (NE, NE)	94.8 (91.6, 98.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dry mouth**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	11 (2.4)
Number of Subjects Censored, n (%)	226 (98.3)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.238 (0.586)
95% CI		(0.393, 3.902)
Log-rank p-value		0.684

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dry mouth**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.0 (96.1, 100.0)	97.4 (95.9, 99.0)
6 months	98.0 (96.1, 100.0)	97.4 (95.9, 99.0)
9 months	98.0 (96.1, 100.0)	97.4 (95.9, 99.0)
12 months	98.0 (96.1, 100.0)	97.4 (95.9, 99.0)
18 months	NE (NE, NE)	97.4 (95.9, 99.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Ascites**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	3 (0.7)
Number of Subjects Censored, n (%)	219 (95.2)	453 (99.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.102 (0.677)
95% CI		(0.027, 0.385)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Ascites**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.8 (91.8, 97.8)	99.5 (98.9, 100.0)
6 months	94.8 (91.8, 97.8)	98.8 (97.3, 100.0)
9 months	94.8 (91.8, 97.8)	98.8 (97.3, 100.0)
12 months	94.8 (91.8, 97.8)	98.8 (97.3, 100.0)
18 months	NE (NE, NE)	98.8 (97.3, 100.0)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dyspepsia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	13 (2.9)
Number of Subjects Censored, n (%)	230 (100.0)	443 (97.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.014

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dyspepsia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	97.2 (95.6, 98.8)
6 months	100.0 (100.0, 100.0)	97.2 (95.6, 98.8)
9 months	100.0 (100.0, 100.0)	95.8 (92.8, 98.9)
12 months	100.0 (100.0, 100.0)	95.8 (92.8, 98.9)
18 months	NE (NE, NE)	95.8 (92.8, 98.9)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	63 (27.4)	196 (43.0)
Number of Subjects Censored, n (%)	167 (72.6)	260 (57.0)
Time to first TEAE (months)		
25% percentile (95% CI)	1.87 (0.95, NE)	1.35 (0.95, 1.64)
Median (95% CI)	10.18 (NE, NE)	6.44 (5.16, NE)
75% percentile (95% CI)	10.18 (NE, NE)	NE (NE, NE)
Min, Max	0.0, 10.2	0.0, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.397 (0.146)
95% CI		(1.049, 1.861)
Log-rank p-value		0.023

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	72.6 (66.6, 78.6)	60.2 (55.6, 64.9)
6 months	67.7 (58.8, 76.6)	53.1 (47.8, 58.5)
9 months	67.7 (58.8, 76.6)	48.5 (42.4, 54.6)
12 months	0.0 (NE, NE)	46.0 (38.6, 53.5)
18 months	0.0 (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.46	2.79

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Decreased appetite**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	40 (17.4)	124 (27.2)
Number of Subjects Censored, n (%)	190 (82.6)	332 (72.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (4.27, NE)	2.92 (1.91, 5.36)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.396 (0.183)
95% CI		(0.974, 2.000)
Log-rank p-value		0.081

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Decreased appetite**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	82.1 (76.9, 87.2)	74.2 (70.0, 78.4)
6 months	79.0 (71.4, 86.7)	70.4 (65.7, 75.1)
9 months	79.0 (71.4, 86.7)	68.0 (62.8, 73.3)
12 months	79.0 (71.4, 86.7)	65.9 (59.4, 72.4)
18 months	NE (NE, NE)	65.9 (59.4, 72.4)
Median Follow-up Time (months)	2.73	2.91

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypokalaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	28 (6.1)
Number of Subjects Censored, n (%)	226 (98.3)	428 (93.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.890 (0.538)
95% CI		(1.008, 8.288)
Log-rank p-value		0.036

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypokalaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.2 (96.5, 99.9)	94.0 (91.7, 96.3)
6 months	98.2 (96.5, 99.9)	93.1 (90.5, 95.7)
9 months	98.2 (96.5, 99.9)	91.9 (88.4, 95.4)
12 months	98.2 (96.5, 99.9)	91.9 (88.4, 95.4)
18 months	NE (NE, NE)	91.9 (88.4, 95.4)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyponatraemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	20 (4.4)
Number of Subjects Censored, n (%)	225 (97.8)	436 (95.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.432 (0.510)
95% CI		(0.527, 3.894)
Log-rank p-value		0.438

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyponatraemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.2 (96.5, 99.9)	96.5 (94.7, 98.2)
6 months	96.5 (92.7, 100.0)	94.4 (91.8, 97.1)
9 months	96.5 (92.7, 100.0)	93.3 (89.9, 96.7)
12 months	96.5 (92.7, 100.0)	93.3 (89.9, 96.7)
18 months	NE (NE, NE)	93.3 (89.9, 96.7)
Median Follow-up Time (months)	2.83	3.76

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperuricaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	14 (3.1)
Number of Subjects Censored, n (%)	226 (98.3)	442 (96.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.464 (0.574)
95% CI		(0.475, 4.507)
Log-rank p-value		0.487

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperuricaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.1 (96.2, 100.0)	97.2 (95.6, 98.8)
6 months	98.1 (96.2, 100.0)	96.8 (95.0, 98.5)
9 months	98.1 (96.2, 100.0)	95.0 (91.2, 98.9)
12 months	98.1 (96.2, 100.0)	95.0 (91.2, 98.9)
18 months	NE (NE, NE)	95.0 (91.2, 98.9)
Median Follow-up Time (months)	2.83	3.76

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypoalbuminaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	15 (3.3)
Number of Subjects Censored, n (%)	227 (98.7)	441 (96.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.145 (0.638)
95% CI		(0.614, 7.496)
Log-rank p-value		0.212

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypoalbuminaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.7 (97.2, 100.0)	96.9 (95.3, 98.6)
6 months	98.7 (97.2, 100.0)	96.3 (94.3, 98.3)
9 months	98.7 (97.2, 100.0)	95.2 (92.1, 98.2)
12 months	98.7 (97.2, 100.0)	95.2 (92.1, 98.2)
18 months	NE (NE, NE)	95.2 (92.1, 98.2)
Median Follow-up Time (months)	2.83	3.76

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypomagnesaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	18 (3.9)
Number of Subjects Censored, n (%)	230 (100.0)	438 (96.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.008

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypomagnesaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	96.8 (95.1, 98.4)
6 months	100.0 (100.0, 100.0)	95.2 (92.7, 97.7)
9 months	100.0 (100.0, 100.0)	94.1 (90.9, 97.3)
12 months	100.0 (100.0, 100.0)	94.1 (90.9, 97.3)
18 months	NE (NE, NE)	94.1 (90.9, 97.3)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Dehydration**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	13 (2.9)
Number of Subjects Censored, n (%)	227 (98.7)	443 (97.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.777 (0.646)
95% CI		(0.501, 6.299)
Log-rank p-value		0.369

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Dehydration**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.3 (96.2, 100.0)	97.2 (95.6, 98.8)
6 months	98.3 (96.2, 100.0)	97.2 (95.6, 98.8)
9 months	98.3 (96.2, 100.0)	96.4 (94.3, 98.6)
12 months	98.3 (96.2, 100.0)	96.4 (94.3, 98.6)
18 months	NE (NE, NE)	96.4 (94.3, 98.6)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperglycaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	13 (2.9)
Number of Subjects Censored, n (%)	228 (99.1)	443 (97.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.349 (0.772)
95% CI		(0.517, 10.667)
Log-rank p-value		0.232

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperglycaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	97.9 (96.6, 99.3)
6 months	99.1 (97.9, 100.0)	96.9 (94.9, 98.9)
9 months	99.1 (97.9, 100.0)	94.4 (90.3, 98.5)
12 months	99.1 (97.9, 100.0)	94.4 (90.3, 98.5)
18 months	NE (NE, NE)	94.4 (90.3, 98.5)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypertriglyceridaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	11 (2.4)
Number of Subjects Censored, n (%)	227 (98.7)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	10.18 (NE, NE)	NE (NE, NE)
Median (95% CI)	10.18 (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	10.18 (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 10.2	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.586 (0.659)
95% CI		(0.436, 5.774)
Log-rank p-value		0.494

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypertriglyceridaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	97.4 (96.0, 98.9)
6 months	99.1 (97.9, 100.0)	97.4 (96.0, 98.9)
9 months	99.1 (97.9, 100.0)	97.4 (96.0, 98.9)
12 months	0.0 (NE, NE)	97.4 (96.0, 98.9)
18 months	0.0 (NE, NE)	97.4 (96.0, 98.9)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypophosphataemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	11 (2.4)
Number of Subjects Censored, n (%)	229 (99.6)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		3.075 (1.057)
95% CI		(0.387, 24.407)
Log-rank p-value		0.262

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypophosphataemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.5, 100.0)	98.7 (97.6, 99.9)
6 months	99.5 (98.5, 100.0)	95.6 (92.9, 98.3)
9 months	99.5 (98.5, 100.0)	95.6 (92.9, 98.3)
12 months	99.5 (98.5, 100.0)	95.6 (92.9, 98.3)
18 months	NE (NE, NE)	95.6 (92.9, 98.3)
Median Follow-up Time (months)	2.83	3.84

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	63 (27.4)	186 (40.8)
Number of Subjects Censored, n (%)	167 (72.6)	270 (59.2)
Time to first TEAE (months)		
25% percentile (95% CI)	1.94 (1.05, 5.59)	1.58 (0.99, 1.68)
Median (95% CI)	NE (5.59, NE)	7.16 (6.01, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (16.79, NE)
Min, Max	0.0, 6.8*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.302 (0.148)
95% CI		(0.975, 1.739)
Log-rank p-value		0.077

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	72.7 (66.7, 78.7)	63.1 (58.5, 67.6)
6 months	54.2 (34.7, 73.7)	55.8 (50.4, 61.2)
9 months	NE (NE, NE)	48.6 (42.1, 55.1)
12 months	NE (NE, NE)	48.6 (42.1, 55.1)
18 months	NE (NE, NE)	36.5 (15.3, 57.7)
Median Follow-up Time (months)	2.61	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Weight decreased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	21 (9.1)	56 (12.3)
Number of Subjects Censored, n (%)	209 (90.9)	400 (87.7)
Time to first TEAE (months)		
25% percentile (95% CI)	5.82 (5.59, NE)	NE (NE, NE)
Median (95% CI)	NE (5.82, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 8.4*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.054 (0.261)
95% CI		(0.632, 1.758)
Log-rank p-value		0.863

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Weight decreased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	89.8 (85.4, 94.3)	89.3 (86.3, 92.2)
6 months	73.7 (51.9, 95.4)	85.7 (81.8, 89.6)
9 months	NE (NE, NE)	82.8 (77.8, 87.8)
12 months	NE (NE, NE)	82.8 (77.8, 87.8)
18 months	NE (NE, NE)	82.8 (77.8, 87.8)
Median Follow-up Time (months)	2.79	3.68

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Aspartate aminotransferase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	48 (10.5)
Number of Subjects Censored, n (%)	219 (95.2)	408 (89.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.59, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 8.4*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.721 (0.339)
95% CI		(0.885, 3.345)
Log-rank p-value		0.113

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Aspartate aminotransferase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.5 (92.8, 98.2)	90.8 (88.0, 93.6)
6 months	89.5 (77.9, 100.0)	87.9 (84.3, 91.5)
9 months	NE (NE, NE)	85.2 (80.6, 89.8)
12 months	NE (NE, NE)	85.2 (80.6, 89.8)
18 months	NE (NE, NE)	85.2 (80.6, 89.8)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Alanine aminotransferase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	9 (3.9)	47 (10.3)
Number of Subjects Censored, n (%)	221 (96.1)	409 (89.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.59, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 8.4*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.039 (0.369)
95% CI		(0.990, 4.203)
Log-rank p-value		0.049

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Alanine aminotransferase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	96.4 (94.0, 98.9)	91.4 (88.7, 94.1)
6 months	90.4 (78.7, 100.0)	88.6 (85.2, 92.0)
9 months	NE (NE, NE)	85.2 (80.5, 89.9)
12 months	NE (NE, NE)	85.2 (80.5, 89.9)
18 months	NE (NE, NE)	85.2 (80.5, 89.9)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood bilirubin increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	36 (7.9)
Number of Subjects Censored, n (%)	219 (95.2)	420 (92.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.269 (0.350)
95% CI		(0.639, 2.520)
Log-rank p-value		0.583

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood bilirubin increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.1 (92.3, 97.9)	93.7 (91.4, 96.0)
6 months	95.1 (92.3, 97.9)	90.7 (87.5, 93.8)
9 months	95.1 (92.3, 97.9)	88.8 (84.7, 92.8)
12 months	95.1 (92.3, 97.9)	88.8 (84.7, 92.8)
18 months	NE (NE, NE)	88.8 (84.7, 92.8)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood thyroid stimulating hormone increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	32 (7.0)
Number of Subjects Censored, n (%)	227 (98.7)	424 (93.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.338 (0.608)
95% CI		(1.318, 14.281)
Log-rank p-value		0.010

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood thyroid stimulating hormone increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.9 (97.5, 100.0)	93.6 (91.3, 96.0)
6 months	96.6 (92.0, 100.0)	92.4 (89.5, 95.3)
9 months	96.6 (92.0, 100.0)	89.2 (84.4, 94.0)
12 months	96.6 (92.0, 100.0)	89.2 (84.4, 94.0)
18 months	NE (NE, NE)	89.2 (84.4, 94.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood alkaline phosphatase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	10 (4.3)	24 (5.3)
Number of Subjects Censored, n (%)	220 (95.7)	432 (94.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.955 (0.383)
95% CI		(0.451, 2.024)
Log-rank p-value		0.840

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood alkaline phosphatase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.1 (92.0, 98.1)	95.4 (93.4, 97.4)
6 months	95.1 (92.0, 98.1)	93.7 (91.0, 96.4)
9 months	95.1 (92.0, 98.1)	92.9 (89.9, 96.0)
12 months	95.1 (92.0, 98.1)	92.9 (89.9, 96.0)
18 months	NE (NE, NE)	92.9 (89.9, 96.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Platelet count decreased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	27 (5.9)
Number of Subjects Censored, n (%)	228 (99.1)	429 (94.1)
Time to first TEAE (months)		
25% percentile (95% CI)	7.43 (7.43, NE)	NE (NE, NE)
Median (95% CI)	7.43 (7.43, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (7.43, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		5.645 (0.736)
95% CI		(1.335, 23.869)
Log-rank p-value		0.008

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Platelet count decreased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	94.4 (92.2, 96.6)
6 months	99.6 (98.7, 100.0)	93.0 (90.3, 95.7)
9 months	NE (NE, NE)	93.0 (90.3, 95.7)
12 months	NE (NE, NE)	93.0 (90.3, 95.7)
18 months	NE (NE, NE)	93.0 (90.3, 95.7)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood creatinine increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	20 (4.4)
Number of Subjects Censored, n (%)	225 (97.8)	436 (95.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.516 (0.507)
95% CI		(0.561, 4.095)
Log-rank p-value		0.419

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood creatinine increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.9 (95.8, 100.0)	96.2 (94.3, 98.0)
6 months	95.7 (90.9, 100.0)	94.6 (92.1, 97.2)
9 months	95.7 (90.9, 100.0)	93.9 (91.1, 96.8)
12 months	95.7 (90.9, 100.0)	93.9 (91.1, 96.8)
18 months	NE (NE, NE)	93.9 (91.1, 96.8)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Amylase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	13 (2.9)
Number of Subjects Censored, n (%)	229 (99.6)	443 (97.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.978 (1.044)
95% CI		(0.644, 38.503)
Log-rank p-value		0.089

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Amylase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.7, 100.0)	97.3 (95.7, 98.9)
6 months	99.5 (98.7, 100.0)	96.8 (94.9, 98.7)
9 months	99.5 (98.7, 100.0)	95.8 (93.1, 98.5)
12 months	99.5 (98.7, 100.0)	95.8 (93.1, 98.5)
18 months	NE (NE, NE)	95.8 (93.1, 98.5)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Lipase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	11 (2.4)
Number of Subjects Censored, n (%)	228 (99.1)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.297 (0.775)
95% CI		(0.503, 10.485)
Log-rank p-value		0.268

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Lipase increased**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	97.6 (96.1, 99.1)
6 months	99.1 (97.9, 100.0)	97.6 (96.1, 99.1)
9 months	99.1 (97.9, 100.0)	96.6 (94.2, 99.0)
12 months	99.1 (97.9, 100.0)	96.6 (94.2, 99.0)
18 months	NE (NE, NE)	96.6 (94.2, 99.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	57 (24.8)	175 (38.4)
Number of Subjects Censored, n (%)	173 (75.2)	281 (61.6)
Time to first TEAE (months)		
25% percentile (95% CI)	2.40 (1.45, NE)	0.85 (0.69, 1.58)
Median (95% CI)	NE (NE, NE)	11.53 (9.07, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.509 (0.154)
95% CI		(1.115, 2.041)
Log-rank p-value		0.009

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	73.5 (67.5, 79.5)	65.2 (60.7, 69.6)
6 months	73.5 (67.5, 79.5)	59.7 (54.6, 64.7)
9 months	73.5 (67.5, 79.5)	56.4 (50.6, 62.2)
12 months	73.5 (67.5, 79.5)	48.2 (37.8, 58.6)
18 months	NE (NE, NE)	48.2 (37.8, 58.6)
Median Follow-up Time (months)	2.40	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dysphonia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	74 (16.2)
Number of Subjects Censored, n (%)	218 (94.8)	382 (83.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1, 13.0*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		3.323 (0.312)
95% CI		(1.802, 6.130)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dysphonia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.3 (91.2, 97.5)	83.7 (80.3, 87.2)
6 months	94.3 (91.2, 97.5)	83.4 (79.9, 86.9)
9 months	94.3 (91.2, 97.5)	83.4 (79.9, 86.9)
12 months	94.3 (91.2, 97.5)	83.4 (79.9, 86.9)
18 months	NE (NE, NE)	83.4 (79.9, 86.9)
Median Follow-up Time (months)	2.81	3.30

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dyspnoea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	22 (9.6)	43 (9.4)
Number of Subjects Censored, n (%)	208 (90.4)	413 (90.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	14.32 (14.32, NE)
Median (95% CI)	NE (NE, NE)	NE (14.32, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.769 (0.268)
95% CI		(0.455, 1.301)
Log-rank p-value		0.319

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dyspnoea**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	90.0 (86.0, 94.0)	92.4 (89.9, 94.9)
6 months	90.0 (86.0, 94.0)	89.7 (86.4, 93.0)
9 months	90.0 (86.0, 94.0)	88.3 (84.5, 92.0)
12 months	90.0 (86.0, 94.0)	85.1 (78.0, 92.2)
18 months	NE (NE, NE)	70.9 (44.9, 97.0)
Median Follow-up Time (months)	2.79	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Cough**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	21 (9.1)	38 (8.3)
Number of Subjects Censored, n (%)	209 (90.9)	418 (91.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (11.53, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.787 (0.276)
95% CI		(0.458, 1.352)
Log-rank p-value		0.387

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Cough**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	90.2 (86.2, 94.2)	92.3 (89.8, 94.8)
6 months	90.2 (86.2, 94.2)	91.4 (88.6, 94.2)
9 months	90.2 (86.2, 94.2)	90.6 (87.5, 93.8)
12 months	90.2 (86.2, 94.2)	85.9 (76.3, 95.4)
18 months	NE (NE, NE)	85.9 (76.3, 95.4)
Median Follow-up Time (months)	2.74	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Epistaxis**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	18 (3.9)
Number of Subjects Censored, n (%)	227 (98.7)	438 (96.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.826 (0.624)
95% CI		(0.832, 9.601)
Log-rank p-value		0.090

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Epistaxis**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.7 (97.2, 100.0)	95.9 (94.0, 97.7)
6 months	98.7 (97.2, 100.0)	95.9 (94.0, 97.7)
9 months	98.7 (97.2, 100.0)	95.9 (94.0, 97.7)
12 months	98.7 (97.2, 100.0)	95.9 (94.0, 97.7)
18 months	NE (NE, NE)	95.9 (94.0, 97.7)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Oropharyngeal pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	10 (2.2)
Number of Subjects Censored, n (%)	228 (99.1)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.805 (0.792)
95% CI		(0.382, 8.529)
Log-rank p-value		0.476

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Oropharyngeal pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.0 (97.7, 100.0)	98.4 (97.3, 99.6)
6 months	99.0 (97.7, 100.0)	97.9 (96.3, 99.5)
9 months	99.0 (97.7, 100.0)	96.1 (93.2, 99.0)
12 months	99.0 (97.7, 100.0)	96.1 (93.2, 99.0)
18 months	NE (NE, NE)	96.1 (93.2, 99.0)
Median Follow-up Time (months)	2.83	3.76

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	34 (14.8)	179 (39.3)
Number of Subjects Censored, n (%)	196 (85.2)	277 (60.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (3.61, NE)	0.95 (0.69, 1.58)
Median (95% CI)	NE (NE, NE)	NE (7.39, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.809 (0.188)
95% CI		(1.944, 4.060)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	84.5 (79.6, 89.4)	61.8 (57.2, 66.4)
6 months	82.0 (75.3, 88.8)	58.2 (53.1, 63.3)
9 months	NE (NE, NE)	53.8 (47.5, 60.1)
12 months	NE (NE, NE)	53.8 (47.5, 60.1)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.61	2.76

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders** and Preferred Term **Hypertension**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	20 (8.7)	168 (36.8)
Number of Subjects Censored, n (%)	210 (91.3)	288 (63.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	0.99 (0.72, 1.61)
Median (95% CI)	NE (NE, NE)	NE (7.39, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.553 (0.237)
95% CI		(2.861, 7.247)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders** and Preferred Term **Hypertension**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	90.5 (86.5, 94.5)	64.1 (59.6, 68.6)
6 months	90.5 (86.5, 94.5)	61.7 (56.9, 66.5)
9 months	NE (NE, NE)	56.1 (49.6, 62.5)
12 months	NE (NE, NE)	56.1 (49.6, 62.5)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.79	2.79

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	48 (20.9)	153 (33.6)
Number of Subjects Censored, n (%)	182 (79.1)	303 (66.4)
Time to first TEAE (months)		
25% percentile (95% CI)	3.71 (2.53, NE)	1.64 (1.05, 2.46)
Median (95% CI)	NE (5.59, NE)	NE (9.76, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.485 (0.167)
95% CI		(1.070, 2.060)
Log-rank p-value		0.015

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	78.8 (73.2, 84.4)	68.3 (63.9, 72.7)
6 months	66.7 (51.1, 82.4)	63.5 (58.3, 68.6)
9 months	NE (NE, NE)	58.1 (51.1, 65.2)
12 months	NE (NE, NE)	55.4 (46.8, 63.9)
18 months	NE (NE, NE)	55.4 (46.8, 63.9)
Median Follow-up Time (months)	2.55	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Back pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	17 (7.4)	47 (10.3)
Number of Subjects Censored, n (%)	213 (92.6)	409 (89.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.153 (0.286)
95% CI		(0.658, 2.021)
Log-rank p-value		0.526

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Back pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	92.3 (88.8, 95.8)	90.6 (87.8, 93.4)
6 months	92.3 (88.8, 95.8)	87.8 (84.3, 91.3)
9 months	92.3 (88.8, 95.8)	87.1 (83.4, 90.9)
12 months	92.3 (88.8, 95.8)	87.1 (83.4, 90.9)
18 months	NE (NE, NE)	87.1 (83.4, 90.9)
Median Follow-up Time (months)	2.79	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Arthralgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	10 (4.3)	50 (11.0)
Number of Subjects Censored, n (%)	220 (95.7)	406 (89.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.59, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.137 (0.350)
95% CI		(1.076, 4.245)
Log-rank p-value		0.029

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Arthralgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.9 (93.2, 98.5)	90.4 (87.6, 93.2)
6 months	89.9 (78.3, 100.0)	87.8 (84.2, 91.4)
9 months	NE (NE, NE)	84.3 (79.0, 89.5)
12 months	NE (NE, NE)	84.3 (79.0, 89.5)
18 months	NE (NE, NE)	84.3 (79.0, 89.5)
Median Follow-up Time (months)	2.83	3.55

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Pain in extremity**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	26 (5.7)
Number of Subjects Censored, n (%)	225 (97.8)	430 (94.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.315 (0.491)
95% CI		(0.884, 6.063)
Log-rank p-value		0.075

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Pain in extremity**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.6 (97.0, 100.0)	94.5 (92.4, 96.7)
6 months	94.0 (87.6, 100.0)	93.3 (90.6, 96.0)
9 months	94.0 (87.6, 100.0)	93.3 (90.6, 96.0)
12 months	94.0 (87.6, 100.0)	93.3 (90.6, 96.0)
18 months	NE (NE, NE)	93.3 (90.6, 96.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Myalgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	14 (3.1)
Number of Subjects Censored, n (%)	225 (97.8)	442 (96.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.242 (0.526)
95% CI		(0.443, 3.481)
Log-rank p-value		0.710

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Myalgia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.7 (95.8, 99.7)	97.0 (95.4, 98.6)
6 months	97.7 (95.8, 99.7)	96.3 (94.2, 98.4)
9 months	97.7 (95.8, 99.7)	96.3 (94.2, 98.4)
12 months	97.7 (95.8, 99.7)	96.3 (94.2, 98.4)
18 months	NE (NE, NE)	96.3 (94.2, 98.4)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Musculoskeletal chest pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	12 (2.6)
Number of Subjects Censored, n (%)	228 (99.1)	444 (97.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.046 (0.782)
95% CI		(0.442, 9.465)
Log-rank p-value		0.340

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Musculoskeletal chest pain**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	98.2 (96.9, 99.4)
6 months	99.1 (97.9, 100.0)	97.5 (95.8, 99.3)
9 months	99.1 (97.9, 100.0)	93.5 (88.6, 98.5)
12 months	99.1 (97.9, 100.0)	93.5 (88.6, 98.5)
18 months	NE (NE, NE)	93.5 (88.6, 98.5)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Muscle spasms**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	11 (2.4)
Number of Subjects Censored, n (%)	230 (100.0)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.031

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Muscle spasms**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	97.4 (95.9, 98.9)
6 months	100.0 (100.0, 100.0)	97.4 (95.9, 98.9)
9 months	100.0 (100.0, 100.0)	97.4 (95.9, 98.9)
12 months	100.0 (100.0, 100.0)	97.4 (95.9, 98.9)
18 months	NE (NE, NE)	97.4 (95.9, 98.9)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	27 (11.7)	157 (34.4)
Number of Subjects Censored, n (%)	203 (88.3)	299 (65.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	1.58 (0.99, 1.84)
Median (95% CI)	NE (NE, NE)	13.14 (13.14, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.994 (0.209)
95% CI		(1.987, 4.512)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	88.3 (84.1, 92.5)	67.4 (63.0, 71.8)
6 months	85.8 (79.6, 92.1)	62.3 (57.2, 67.5)
9 months	85.8 (79.6, 92.1)	60.2 (54.4, 66.0)
12 months	85.8 (79.6, 92.1)	60.2 (54.4, 66.0)
18 months	NE (NE, NE)	45.1 (19.2, 71.0)
Median Follow-up Time (months)	2.78	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Palmar-plantar erythrodysaesthesia syndrome**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	6 (2.6)	88 (19.3)
Number of Subjects Censored, n (%)	224 (97.4)	368 (80.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (4.60, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		7.215 (0.423)
95% CI		(3.151, 16.522)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Palmar-plantar erythrodysaesthesia syndrome**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.3 (95.2, 99.4)	82.4 (78.8, 86.0)
6 months	97.3 (95.2, 99.4)	77.8 (73.3, 82.3)
9 months	97.3 (95.2, 99.4)	76.5 (71.5, 81.6)
12 months	97.3 (95.2, 99.4)	76.5 (71.5, 81.6)
18 months	NE (NE, NE)	76.5 (71.5, 81.6)
Median Follow-up Time (months)	2.83	3.04

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Rash**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	8 (3.5)	18 (3.9)
Number of Subjects Censored, n (%)	222 (96.5)	438 (96.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.060 (0.426)
95% CI		(0.459, 2.444)
Log-rank p-value		0.904

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Rash**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	96.5 (94.0, 98.9)	95.9 (94.0, 97.8)
6 months	96.5 (94.0, 98.9)	95.9 (94.0, 97.8)
9 months	96.5 (94.0, 98.9)	95.9 (94.0, 97.8)
12 months	96.5 (94.0, 98.9)	95.9 (94.0, 97.8)
18 months	NE (NE, NE)	95.9 (94.0, 97.8)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Dry skin**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	13 (2.9)
Number of Subjects Censored, n (%)	227 (98.7)	443 (97.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.951 (0.644)
95% CI		(0.552, 6.899)
Log-rank p-value		0.315

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Dry skin**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.7, 100.0)	97.2 (95.7, 98.8)
6 months	96.7 (92.1, 100.0)	96.8 (95.1, 98.6)
9 months	96.7 (92.1, 100.0)	96.8 (95.1, 98.6)
12 months	96.7 (92.1, 100.0)	96.8 (95.1, 98.6)
18 months	NE (NE, NE)	96.8 (95.1, 98.6)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	37 (16.1)	115 (25.2)
Number of Subjects Censored, n (%)	193 (83.9)	341 (74.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	4.57 (2.40, 6.21)
Median (95% CI)	NE (NE, NE)	18.04 (18.04, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.396 (0.191)
95% CI		(0.960, 2.029)
Log-rank p-value		0.096

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	82.6 (77.4, 87.8)	77.5 (73.6, 81.4)
6 months	82.6 (77.4, 87.8)	71.5 (66.5, 76.4)
9 months	82.6 (77.4, 87.8)	70.0 (64.7, 75.2)
12 months	82.6 (77.4, 87.8)	66.7 (58.6, 74.8)
18 months	NE (NE, NE)	66.7 (58.6, 74.8)
Median Follow-up Time (months)	2.60	2.99

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Headache**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	41 (9.0)
Number of Subjects Censored, n (%)	219 (95.2)	415 (91.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	18.04 (18.04, NE)
Median (95% CI)	NE (NE, NE)	NE (18.04, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (18.04, NE)
Min, Max	0.1, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.698 (0.343)
95% CI		(0.868, 3.324)
Log-rank p-value		0.122

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Headache**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.7 (91.6, 97.8)	92.0 (89.5, 94.5)
6 months	94.7 (91.6, 97.8)	91.0 (88.1, 93.8)
9 months	94.7 (91.6, 97.8)	89.5 (86.0, 92.9)
12 months	94.7 (91.6, 97.8)	89.5 (86.0, 92.9)
18 months	NE (NE, NE)	89.5 (86.0, 92.9)
Median Follow-up Time (months)	2.83	3.68

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dysgeusia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	7 (3.0)	10 (2.2)
Number of Subjects Censored, n (%)	223 (97.0)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.658 (0.494)
95% CI		(0.250, 1.732)
Log-rank p-value		0.380

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dysgeusia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	96.9 (94.6, 99.2)	97.7 (96.3, 99.1)
6 months	96.9 (94.6, 99.2)	97.7 (96.3, 99.1)
9 months	96.9 (94.6, 99.2)	97.7 (96.3, 99.1)
12 months	96.9 (94.6, 99.2)	97.7 (96.3, 99.1)
18 months	NE (NE, NE)	97.7 (96.3, 99.1)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dizziness**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	12 (2.6)
Number of Subjects Censored, n (%)	226 (98.3)	444 (97.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.478 (0.578)
95% CI		(0.476, 4.587)
Log-rank p-value		0.507

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dizziness**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.1 (96.3, 99.9)	97.3 (95.8, 98.8)
6 months	98.1 (96.3, 99.9)	97.3 (95.8, 98.8)
9 months	98.1 (96.3, 99.9)	97.3 (95.8, 98.8)
12 months	98.1 (96.3, 99.9)	97.3 (95.8, 98.8)
18 months	NE (NE, NE)	97.3 (95.8, 98.8)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	30 (13.0)	112 (24.6)
Number of Subjects Censored, n (%)	200 (87.0)	344 (75.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	4.57 (2.83, 6.54)
Median (95% CI)	NE (NE, NE)	13.60 (11.96, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.60, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.564 (0.208)
95% CI		(1.040, 2.351)
Log-rank p-value		0.040

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	86.1 (81.3, 90.9)	78.7 (74.8, 82.6)
6 months	83.7 (77.1, 90.2)	71.5 (66.4, 76.5)
9 months	83.7 (77.1, 90.2)	68.7 (63.0, 74.5)
12 months	83.7 (77.1, 90.2)	61.8 (48.1, 75.6)
18 months	NE (NE, NE)	46.4 (18.2, 74.6)
Median Follow-up Time (months)	2.74	3.06

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Proteinuria**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	79 (17.3)
Number of Subjects Censored, n (%)	218 (94.8)	377 (82.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.60 (6.93, NE)
Median (95% CI)	NE (NE, NE)	NE (13.60, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.60, NE)
Min, Max	0.2*, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.812 (0.312)
95% CI		(1.526, 5.183)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Proteinuria**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.4 (91.4, 97.5)	84.5 (81.0, 88.0)
6 months	94.4 (91.4, 97.5)	79.9 (75.6, 84.3)
9 months	94.4 (91.4, 97.5)	77.2 (71.6, 82.9)
12 months	94.4 (91.4, 97.5)	77.2 (71.6, 82.9)
18 months	NE (NE, NE)	57.9 (24.9, 91.0)
Median Follow-up Time (months)	2.79	3.33

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Haematuria**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	10 (2.2)
Number of Subjects Censored, n (%)	225 (97.8)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.849 (0.553)
95% CI		(0.287, 2.510)
Log-rank p-value		0.737

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Haematuria**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.7 (95.7, 99.7)	98.0 (96.7, 99.3)
6 months	97.7 (95.7, 99.7)	97.5 (96.0, 99.1)
9 months	97.7 (95.7, 99.7)	97.5 (96.0, 99.1)
12 months	97.7 (95.7, 99.7)	97.5 (96.0, 99.1)
18 months	NE (NE, NE)	97.5 (96.0, 99.1)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	29 (12.6)	96 (21.1)
Number of Subjects Censored, n (%)	201 (87.4)	360 (78.9)
Time to first TEAE (months)		
25% percentile (95% CI)	5.78 (4.34, NE)	5.91 (4.63, 7.69)
Median (95% CI)	NE (5.78, NE)	17.48 (11.53, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (17.48, NE)
Min, Max	0.0, 13.0*	0.1, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.153 (0.219)
95% CI		(0.751, 1.769)
Log-rank p-value		0.438

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	88.3 (83.9, 92.6)	84.5 (81.0, 88.0)
6 months	70.3 (49.9, 90.6)	74.7 (69.4, 80.0)
9 months	70.3 (49.9, 90.6)	65.2 (57.6, 72.8)
12 months	70.3 (49.9, 90.6)	60.9 (50.0, 71.7)
18 months	NE (NE, NE)	45.6 (18.6, 72.7)
Median Follow-up Time (months)	2.79	3.30

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Urinary tract infection**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	8 (3.5)	19 (4.2)
Number of Subjects Censored, n (%)	222 (96.5)	437 (95.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (4.34, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.750 (0.441)
95% CI		(0.316, 1.778)
Log-rank p-value		0.620

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Urinary tract infection**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.2 (96.5, 100.0)	97.0 (95.4, 98.6)
6 months	87.6 (77.1, 98.0)	95.2 (92.6, 97.8)
9 months	87.6 (77.1, 98.0)	92.6 (88.8, 96.5)
12 months	87.6 (77.1, 98.0)	92.6 (88.8, 96.5)
18 months	NE (NE, NE)	92.6 (88.8, 96.5)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **COVID-19**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	6 (2.6)	12 (2.6)
Number of Subjects Censored, n (%)	224 (97.4)	444 (97.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.520 (0.526)
95% CI		(0.185, 1.460)
Log-rank p-value		0.191

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **COVID-19**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.5 (95.4, 99.7)	98.8 (97.7, 99.8)
6 months	94.1 (87.0, 100.0)	96.4 (94.0, 98.7)
9 months	94.1 (87.0, 100.0)	95.5 (92.7, 98.4)
12 months	94.1 (87.0, 100.0)	90.8 (81.2, 100.0)
18 months	NE (NE, NE)	90.8 (81.2, 100.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Pneumonia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	11 (2.4)
Number of Subjects Censored, n (%)	229 (99.6)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.245 (1.049)
95% CI		(0.543, 33.152)
Log-rank p-value		0.139

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Pneumonia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	97.5 (95.9, 99.1)
6 months	99.6 (98.7, 100.0)	96.8 (94.8, 98.8)
9 months	99.6 (98.7, 100.0)	96.8 (94.8, 98.8)
12 months	99.6 (98.7, 100.0)	96.8 (94.8, 98.8)
18 months	NE (NE, NE)	96.8 (94.8, 98.8)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	37 (16.1)	67 (14.7)
Number of Subjects Censored, n (%)	193 (83.9)	389 (85.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (6.77, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.749 (0.209)
95% CI		(0.497, 1.127)
Log-rank p-value		0.185

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	82.2 (76.8, 87.5)	87.0 (83.8, 90.2)
6 months	82.2 (76.8, 87.5)	82.9 (78.7, 87.1)
9 months	82.2 (76.8, 87.5)	80.4 (75.4, 85.3)
12 months	82.2 (76.8, 87.5)	80.4 (75.4, 85.3)
18 months	NE (NE, NE)	80.4 (75.4, 85.3)
Median Follow-up Time (months)	2.74	3.55

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Anaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	28 (12.2)	36 (7.9)
Number of Subjects Censored, n (%)	202 (87.8)	420 (92.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	17.74 (17.74, NE)
Median (95% CI)	NE (NE, NE)	NE (17.74, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (17.74, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.460 (0.261)
95% CI		(0.276, 0.769)
Log-rank p-value		0.003

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Anaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	86.1 (81.1, 91.0)	94.1 (91.8, 96.3)
6 months	86.1 (81.1, 91.0)	90.0 (86.4, 93.6)
9 months	86.1 (81.1, 91.0)	88.5 (84.4, 92.6)
12 months	86.1 (81.1, 91.0)	88.5 (84.4, 92.6)
18 months	NE (NE, NE)	59.0 (11.7, 100.0)
Median Follow-up Time (months)	2.78	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Thrombocytopenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	30 (6.6)
Number of Subjects Censored, n (%)	227 (98.7)	426 (93.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 18.6*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.890 (0.606)
95% CI		(1.491, 16.037)
Log-rank p-value		0.004

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Thrombocytopenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.6 (97.1, 100.0)	93.1 (90.7, 95.5)
6 months	98.6 (97.1, 100.0)	93.1 (90.7, 95.5)
9 months	98.6 (97.1, 100.0)	93.1 (90.7, 95.5)
12 months	98.6 (97.1, 100.0)	93.1 (90.7, 95.5)
18 months	NE (NE, NE)	93.1 (90.7, 95.5)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	100 (21.9)
Number of Subjects Censored, n (%)	229 (99.6)	356 (78.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	5.52 (3.84, 6.47)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6, 16.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		41.560 (1.006)
95% CI		(5.789, 298.339)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	82.1 (78.4, 85.7)
6 months	99.6 (98.7, 100.0)	71.0 (65.3, 76.7)
9 months	99.6 (98.7, 100.0)	68.3 (62.0, 74.5)
12 months	99.6 (98.7, 100.0)	65.7 (58.0, 73.5)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.83	3.06

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders** and Preferred Term **Hypothyroidism**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	94 (20.6)
Number of Subjects Censored, n (%)	229 (99.6)	362 (79.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	5.75 (4.17, 9.33)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6, 16.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		38.183 (1.006)
95% CI		(5.314, 274.346)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders** and Preferred Term **Hypothyroidism**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	83.5 (79.9, 87.0)
6 months	99.6 (98.7, 100.0)	73.0 (67.5, 78.6)
9 months	99.6 (98.7, 100.0)	69.0 (62.5, 75.5)
12 months	99.6 (98.7, 100.0)	66.6 (58.7, 74.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.83	3.19

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	17 (7.4)	58 (12.7)
Number of Subjects Censored, n (%)	213 (92.6)	398 (87.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.339 (0.279)
95% CI		(0.775, 2.313)
Log-rank p-value		0.288

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	92.4 (88.8, 96.0)	88.9 (85.9, 92.0)
6 months	90.8 (86.1, 95.5)	83.8 (79.6, 88.0)
9 months	90.8 (86.1, 95.5)	82.9 (78.4, 87.4)
12 months	90.8 (86.1, 95.5)	82.9 (78.4, 87.4)
18 months	NE (NE, NE)	82.9 (78.4, 87.4)
Median Follow-up Time (months)	2.79	3.68

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Insomnia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	26 (5.7)
Number of Subjects Censored, n (%)	218 (94.8)	430 (94.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.787 (0.354)
95% CI		(0.394, 1.574)
Log-rank p-value		0.522

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Insomnia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.4 (91.2, 97.5)	94.9 (92.8, 97.1)
6 months	94.4 (91.2, 97.5)	92.8 (89.9, 95.6)
9 months	94.4 (91.2, 97.5)	91.9 (88.5, 95.2)
12 months	94.4 (91.2, 97.5)	91.9 (88.5, 95.2)
18 months	NE (NE, NE)	91.9 (88.5, 95.2)
Median Follow-up Time (months)	2.81	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Anxiety**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	11 (2.4)
Number of Subjects Censored, n (%)	228 (99.1)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.242 (0.774)
95% CI		(0.492, 10.231)
Log-rank p-value		0.322

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Anxiety**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.5, 100.0)	97.5 (95.9, 99.1)
6 months	97.8 (94.5, 100.0)	96.9 (95.0, 98.8)
9 months	97.8 (94.5, 100.0)	96.9 (95.0, 98.8)
12 months	97.8 (94.5, 100.0)	96.9 (95.0, 98.8)
18 months	NE (NE, NE)	96.9 (95.0, 98.8)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Confusional state**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	11 (2.4)
Number of Subjects Censored, n (%)	228 (99.1)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.316 (0.775)
95% CI		(0.507, 10.571)
Log-rank p-value		0.267

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Confusional state**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.0 (97.5, 100.0)	97.9 (96.5, 99.3)
6 months	99.0 (97.5, 100.0)	96.9 (94.9, 98.8)
9 months	99.0 (97.5, 100.0)	96.9 (94.9, 98.8)
12 months	99.0 (97.5, 100.0)	96.9 (94.9, 98.8)
18 months	NE (NE, NE)	96.9 (94.9, 98.8)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	24 (10.4)	50 (11.0)
Number of Subjects Censored, n (%)	206 (89.6)	406 (89.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.805 (0.253)
95% CI		(0.490, 1.321)
Log-rank p-value		0.416

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	89.6 (85.5, 93.6)	90.2 (87.4, 93.1)
6 months	88.0 (83.1, 93.0)	86.7 (82.9, 90.5)
9 months	88.0 (83.1, 93.0)	85.6 (81.2, 89.9)
12 months	88.0 (83.1, 93.0)	83.3 (77.1, 89.4)
18 months	NE (NE, NE)	83.3 (77.1, 89.4)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders** and Preferred Term **Hypertransaminasaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	19 (4.2)
Number of Subjects Censored, n (%)	227 (98.7)	437 (95.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.350 (0.627)
95% CI		(0.688, 8.030)
Log-rank p-value		0.174

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders** and Preferred Term **Hypertransaminasaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.5 (96.9, 100.0)	96.0 (94.1, 97.9)
6 months	98.5 (96.9, 100.0)	94.9 (92.5, 97.4)
9 months	98.5 (96.9, 100.0)	94.9 (92.5, 97.4)
12 months	98.5 (96.9, 100.0)	92.4 (86.9, 97.9)
18 months	NE (NE, NE)	92.4 (86.9, 97.9)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders** and Preferred Term **Hyperbilirubinaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	14 (3.1)
Number of Subjects Censored, n (%)	228 (99.1)	442 (96.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.568 (0.764)
95% CI		(0.575, 11.480)
Log-rank p-value		0.200

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.1.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders** and Preferred Term **Hyperbilirubinaemia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	97.4 (96.0, 98.9)
6 months	99.1 (97.9, 100.0)	96.4 (94.3, 98.5)
9 months	99.1 (97.9, 100.0)	95.2 (92.1, 98.3)
12 months	99.1 (97.9, 100.0)	95.2 (92.1, 98.3)
18 months	NE (NE, NE)	95.2 (92.1, 98.3)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

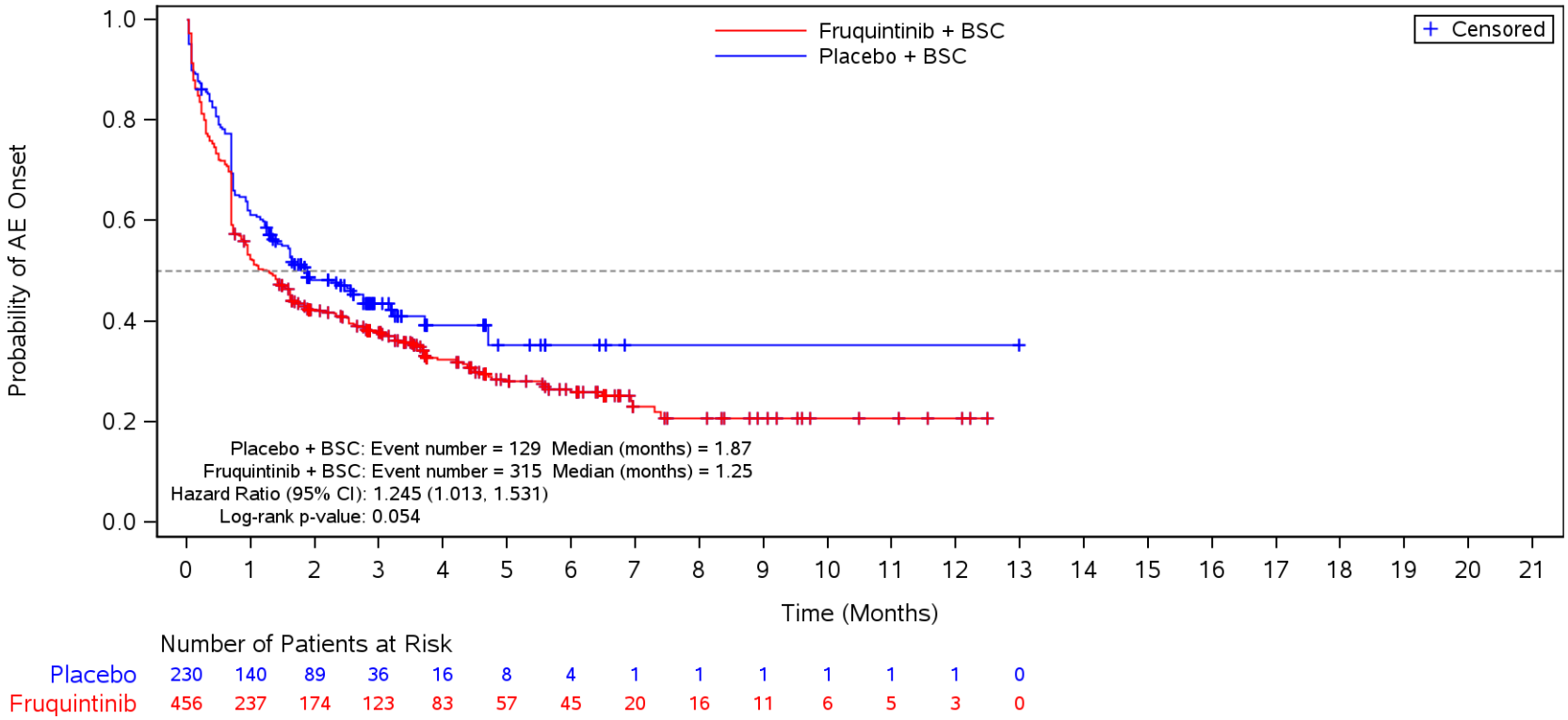
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

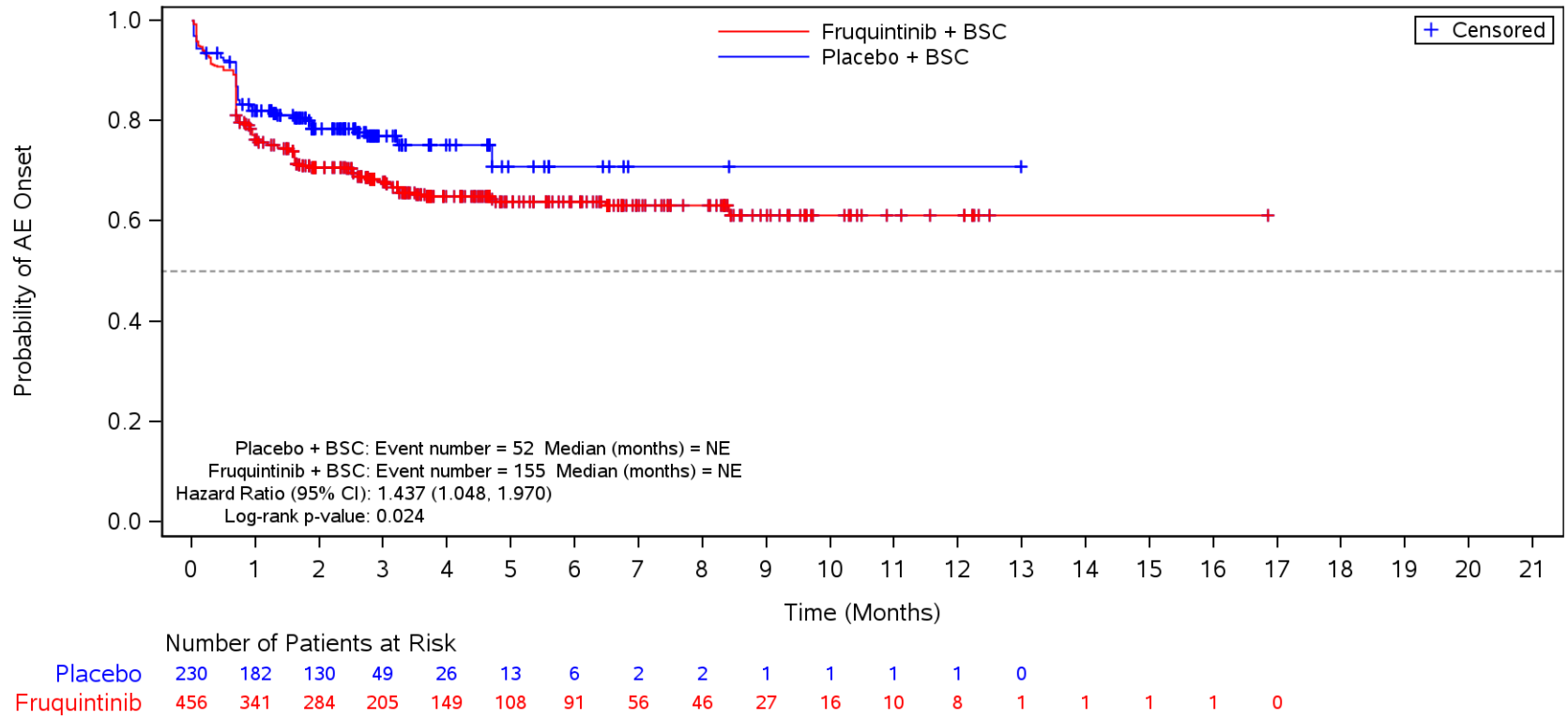
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions**



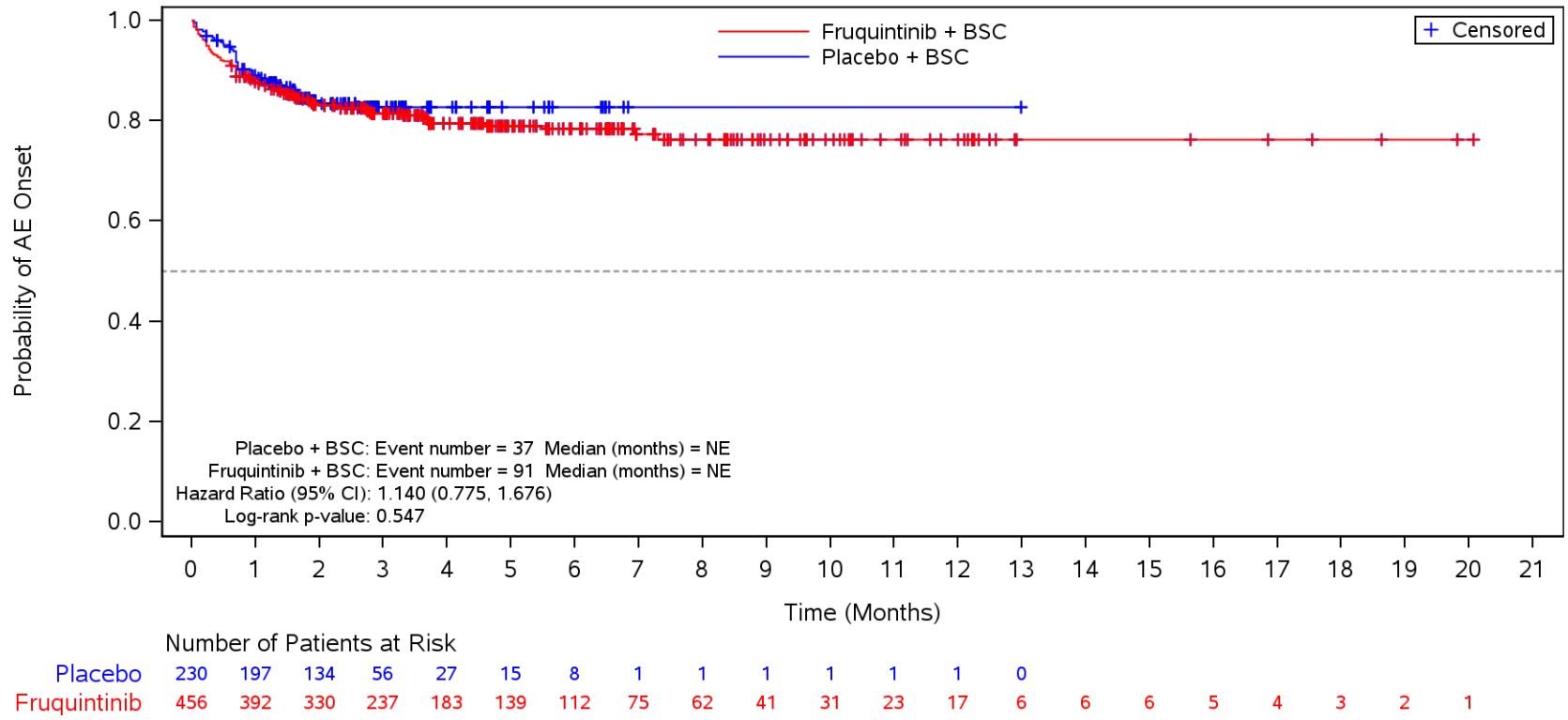
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**



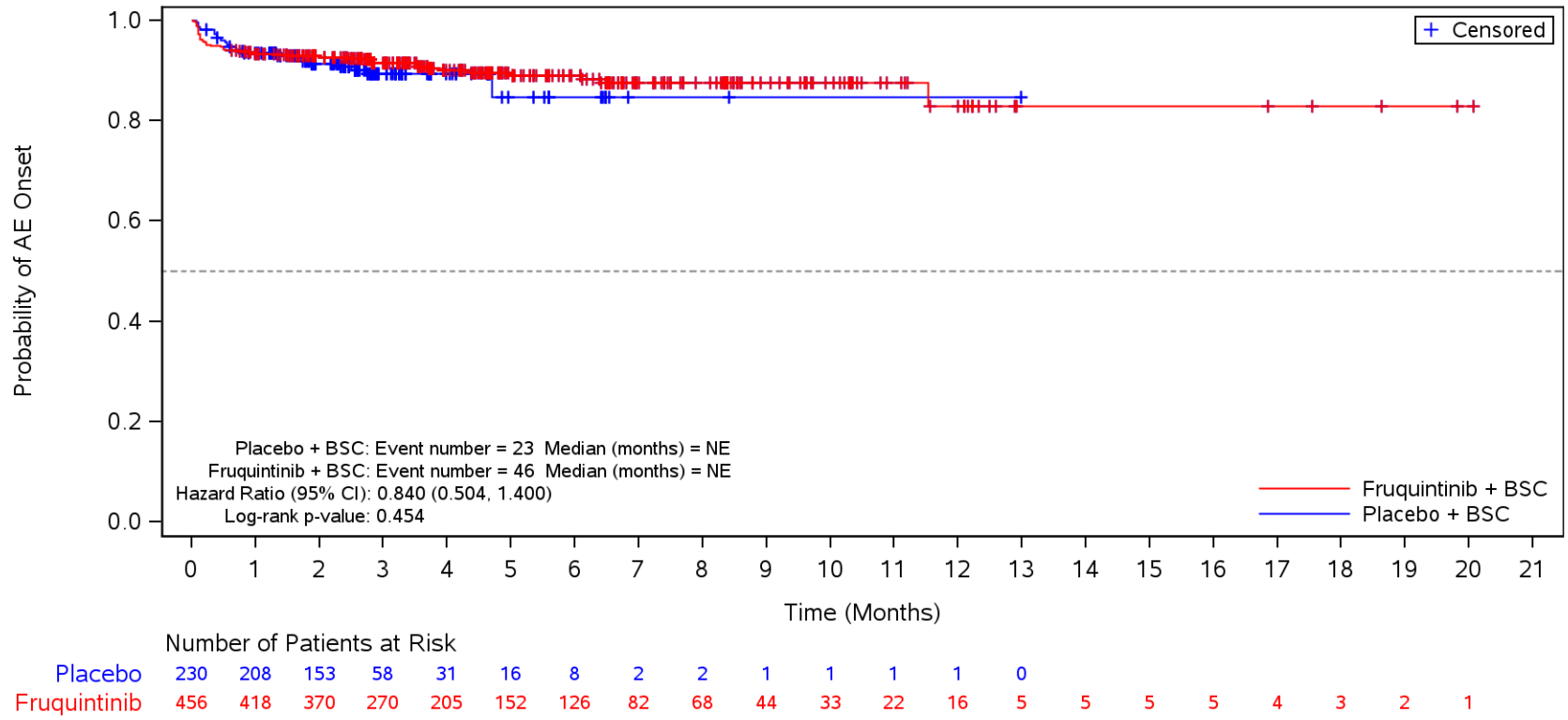
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Fatigue**



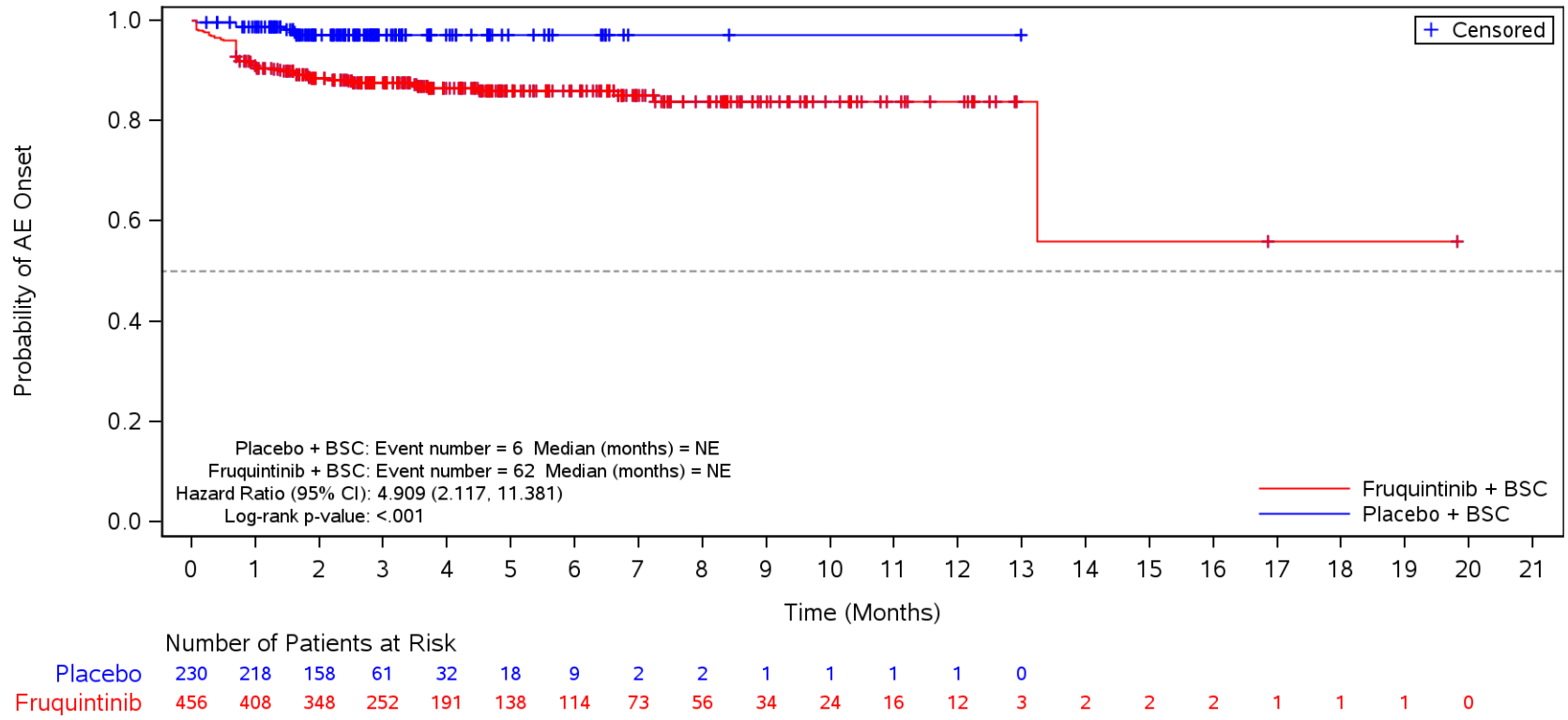
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Pyrexia**



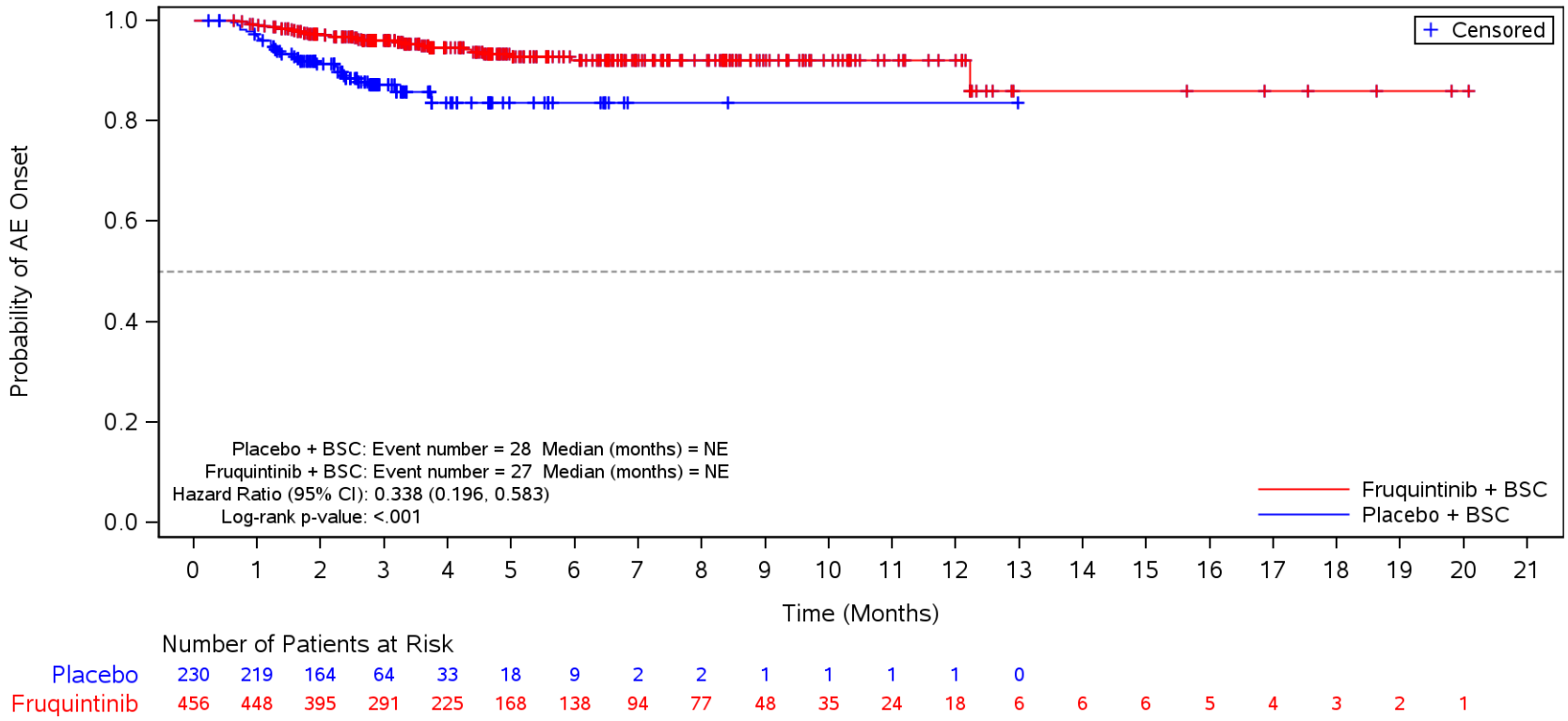
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Mucosal inflammation**



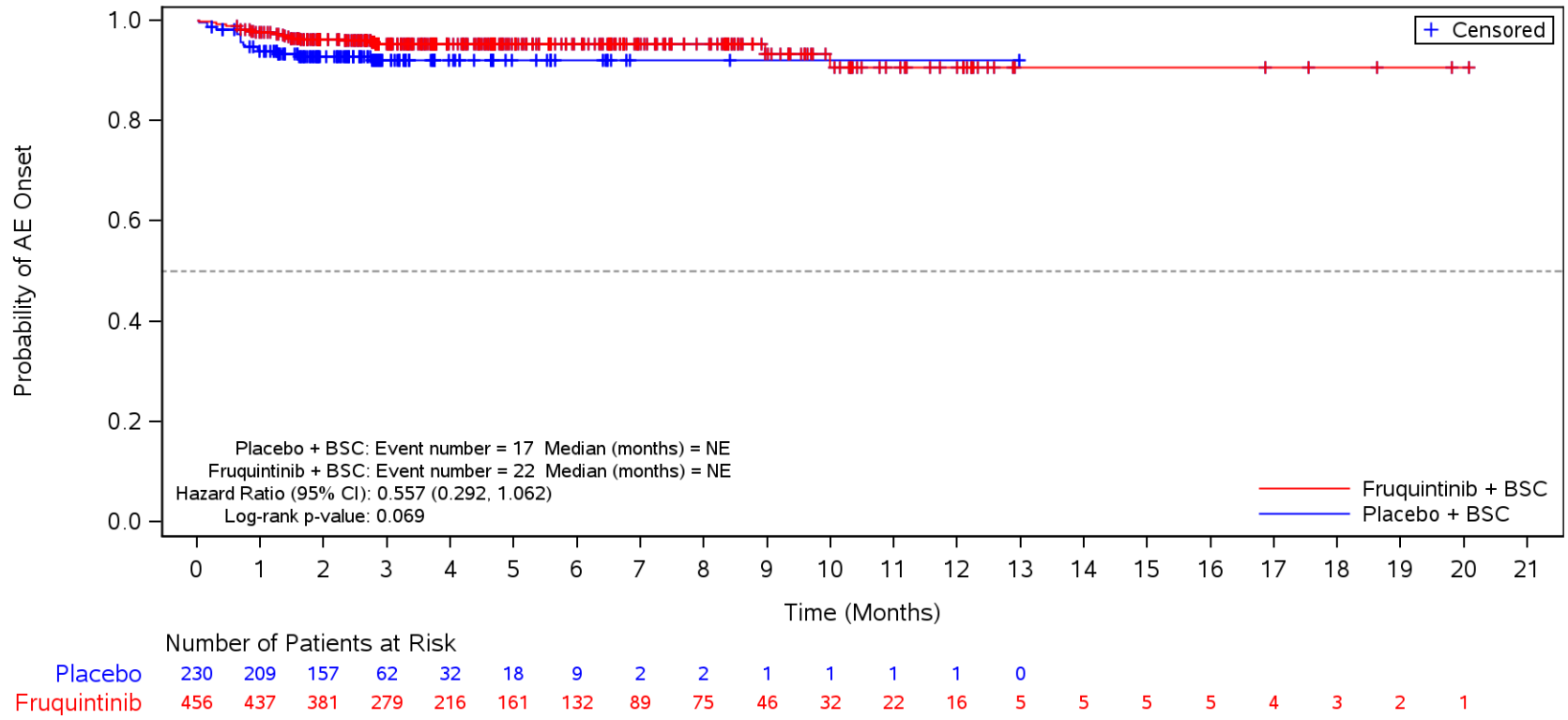
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**



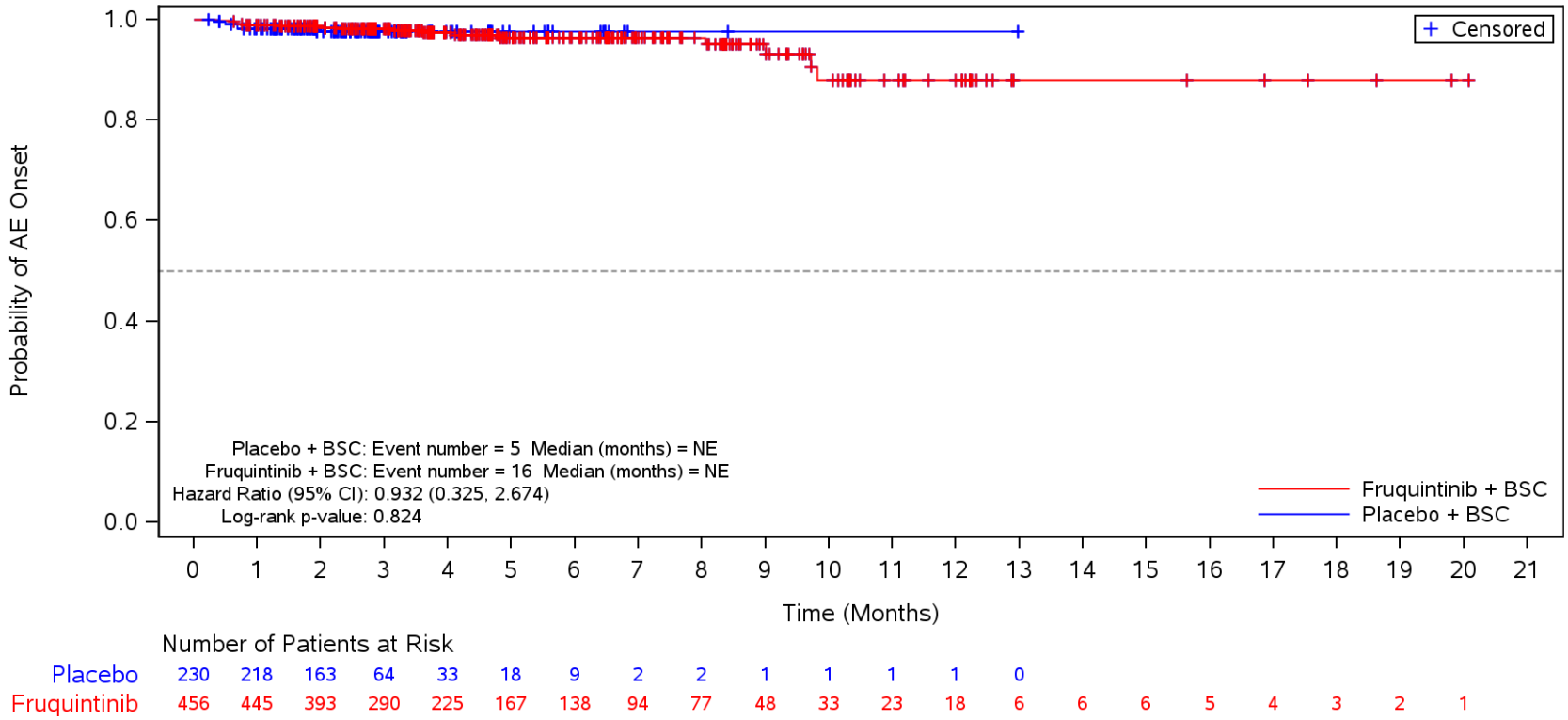
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Oedema peripheral**



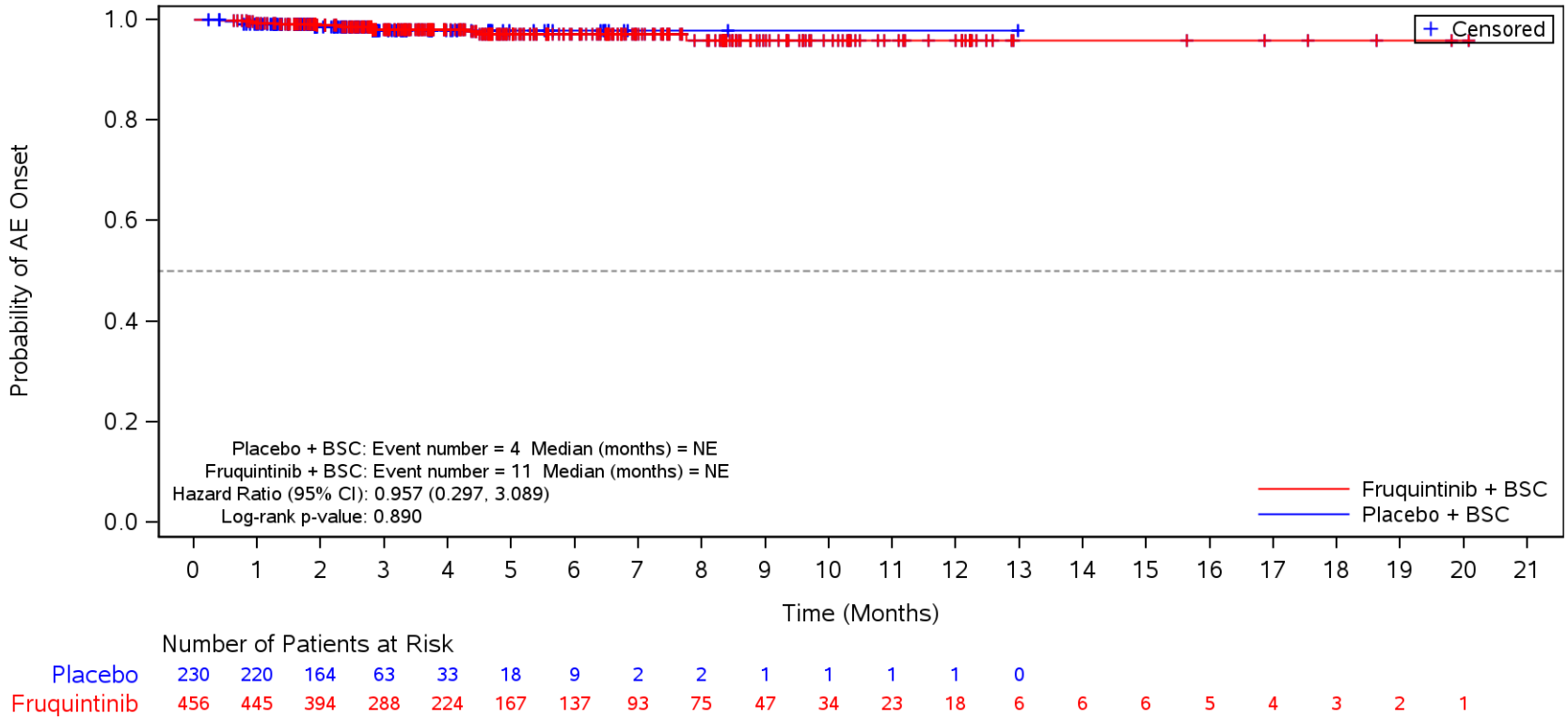
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **General physical health deterioration**



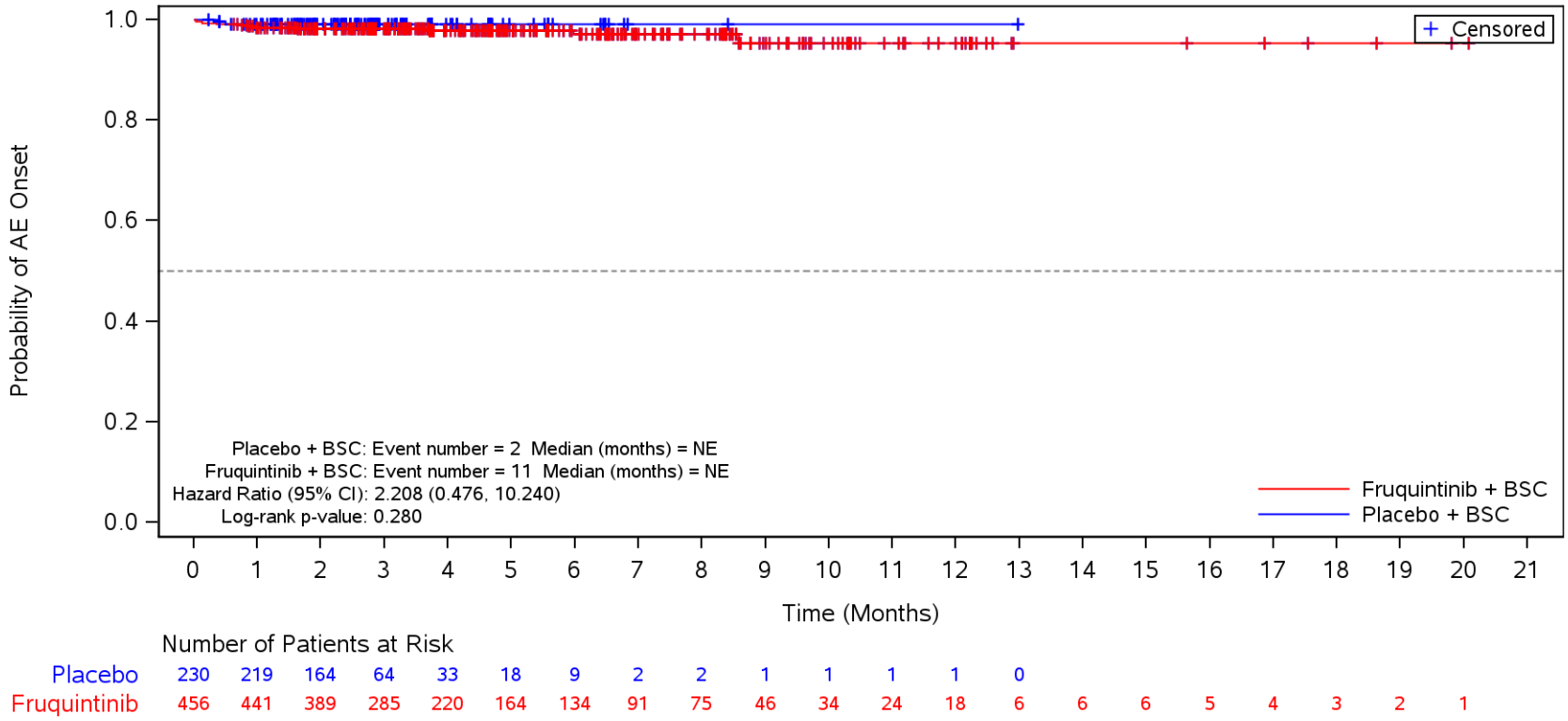
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Condition aggravated**



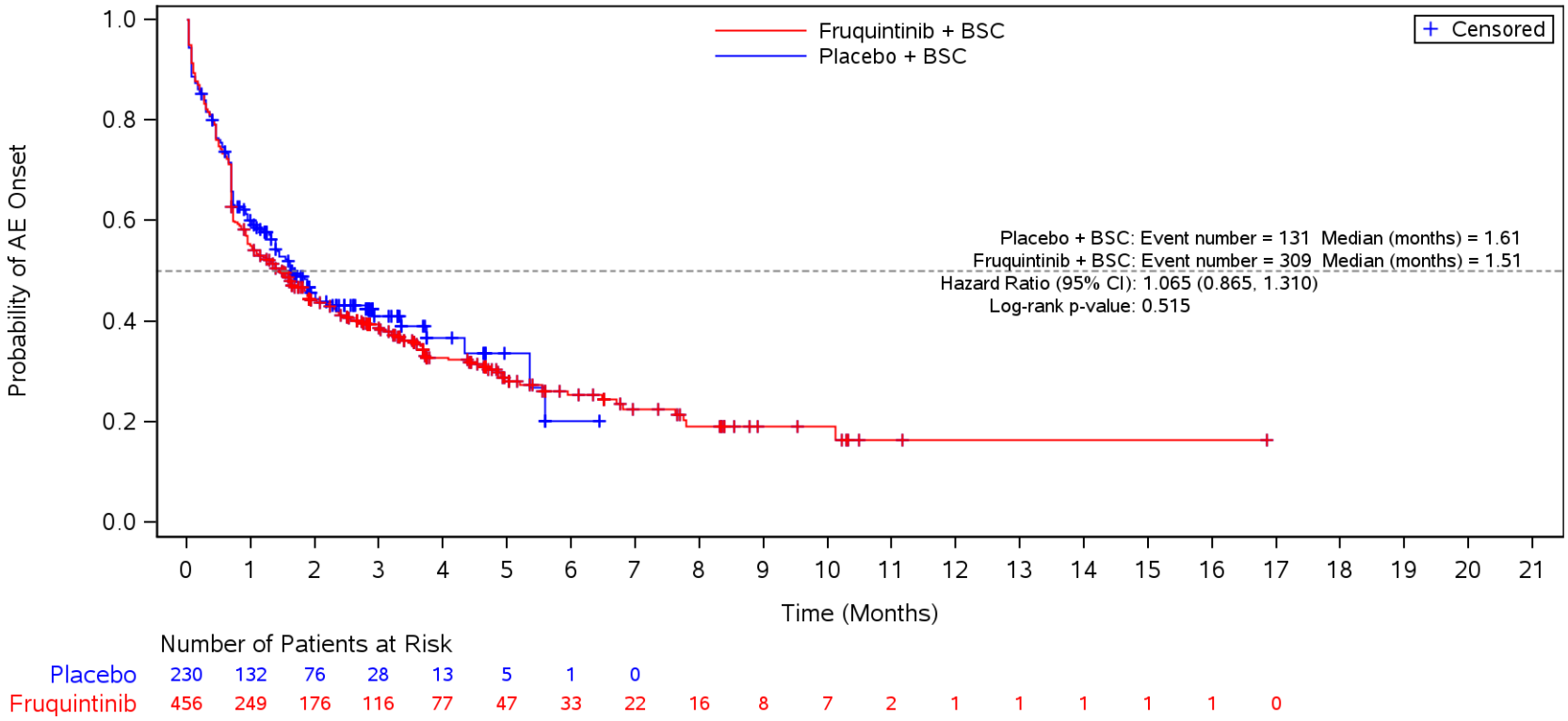
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **General disorders and administration site conditions** and Preferred Term **Chills**



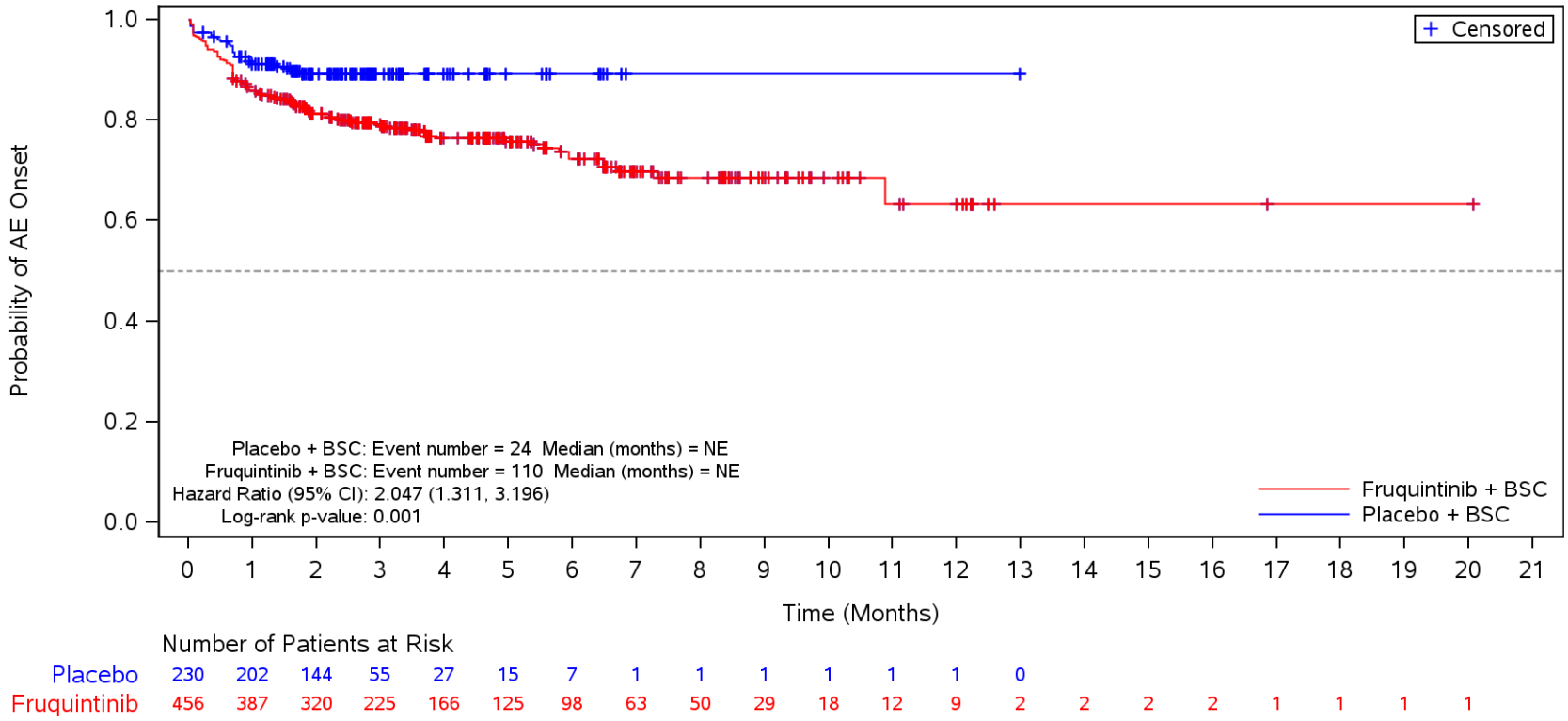
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders**



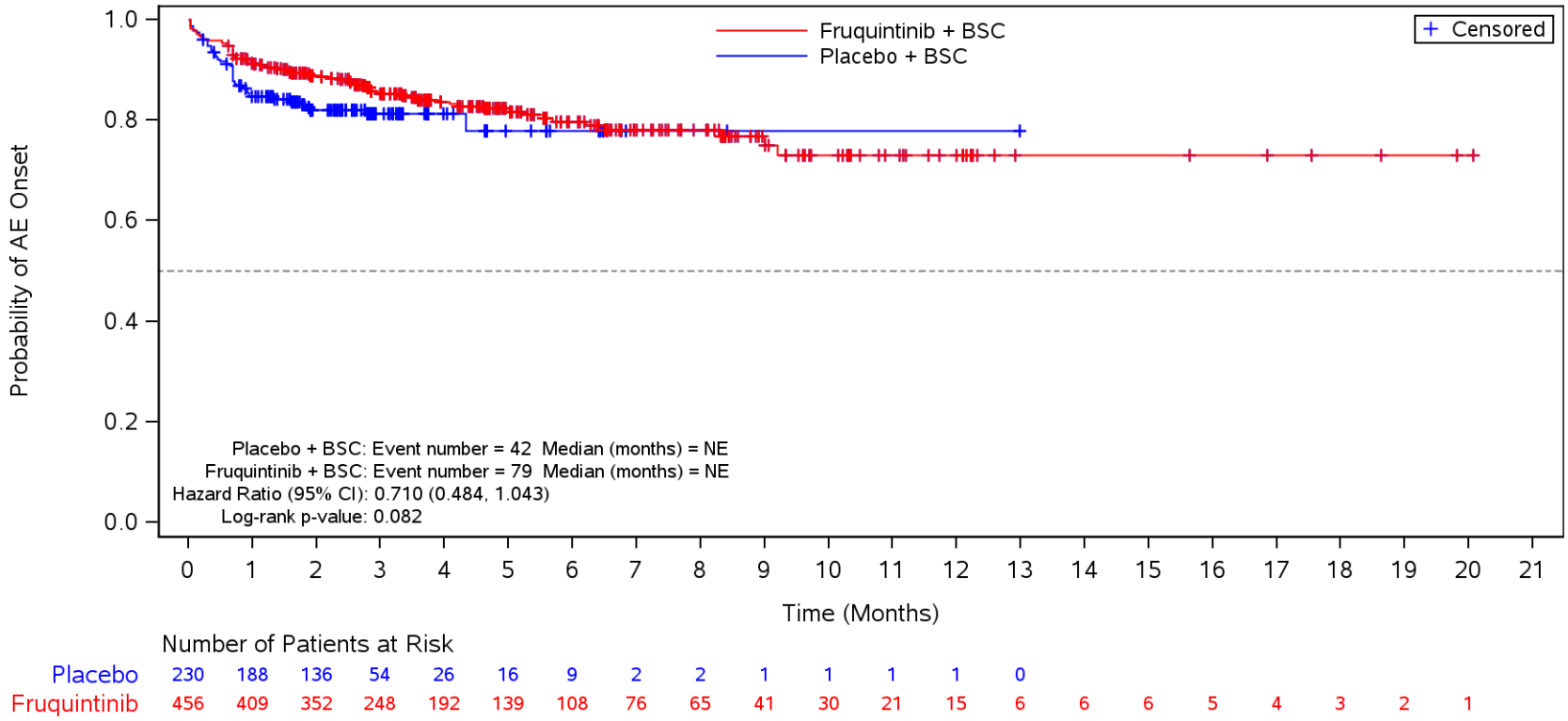
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Diarrhoea**



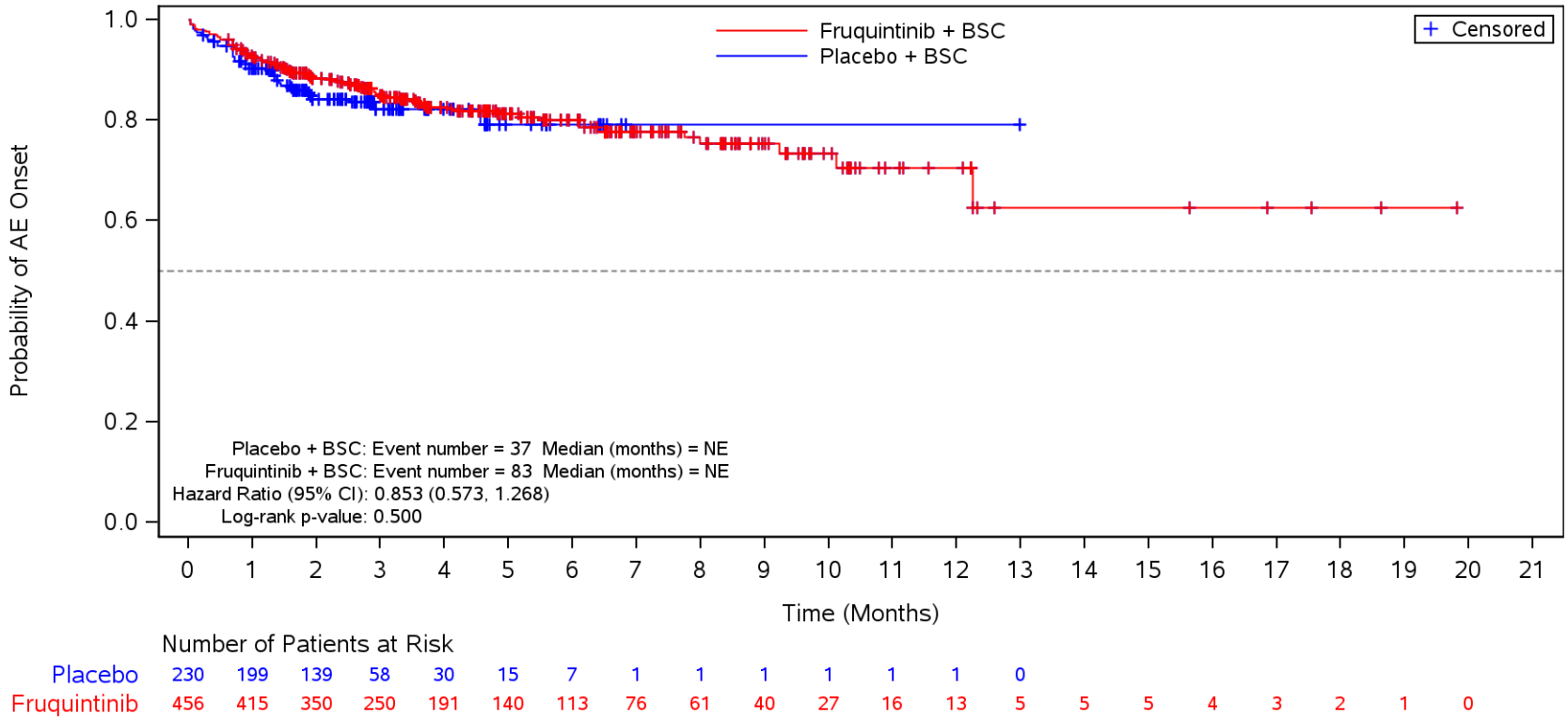
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Nausea**



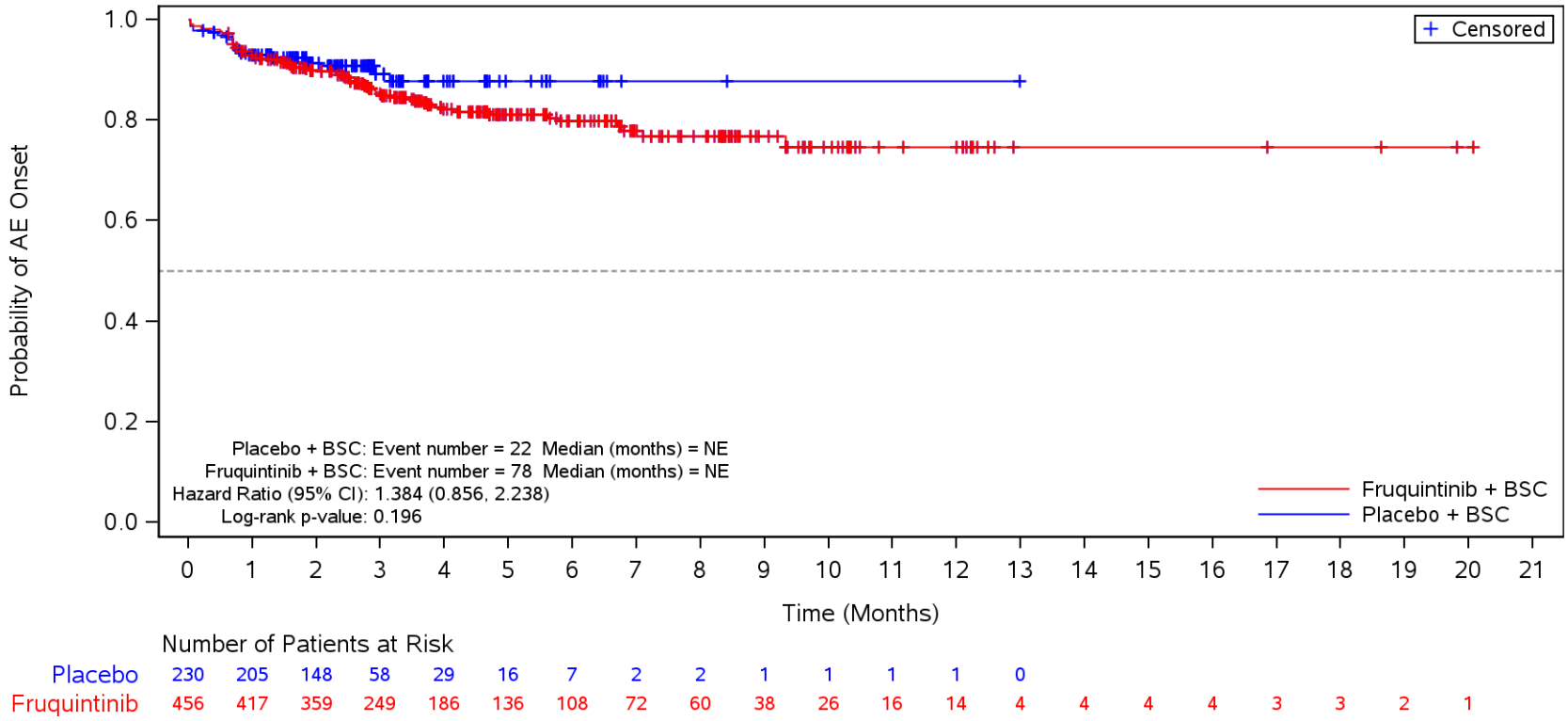
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain**



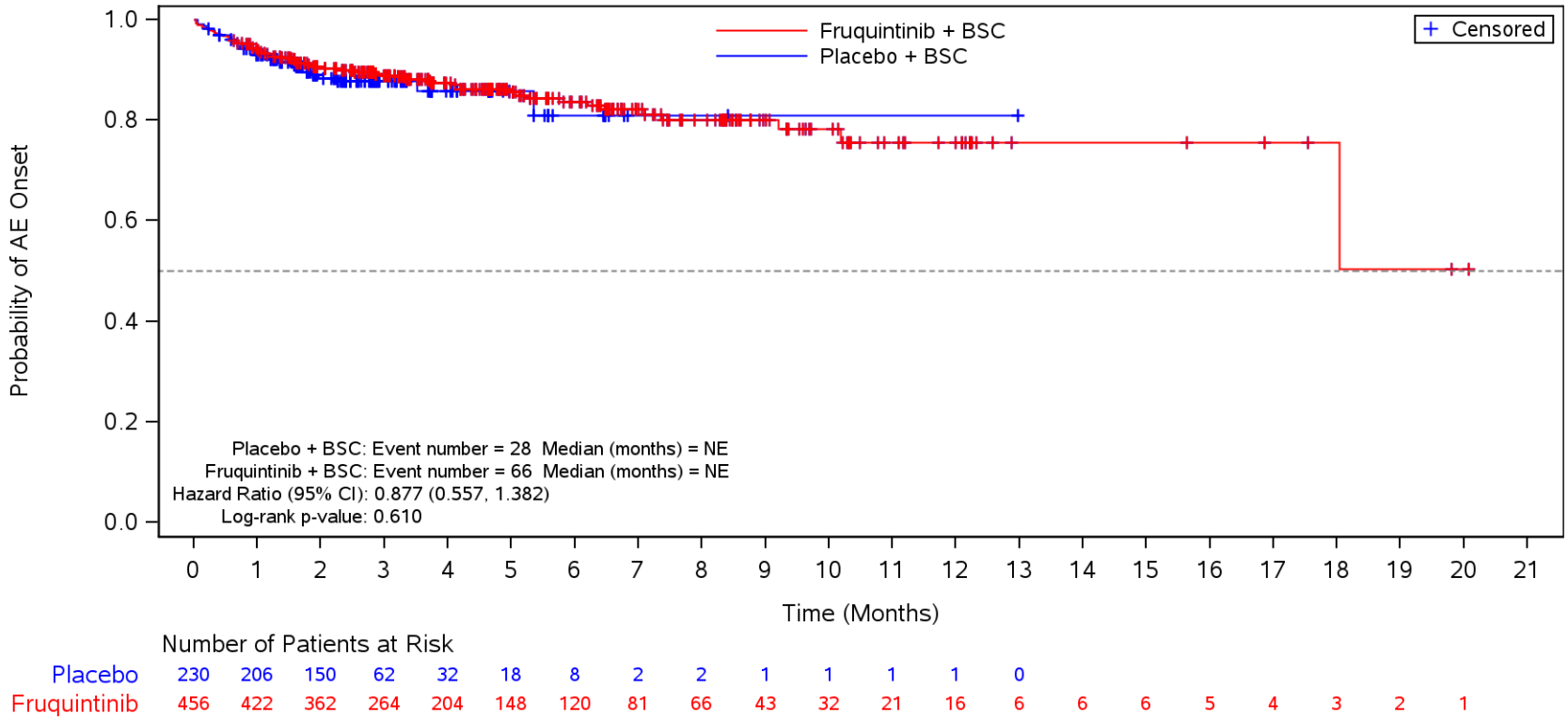
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Constipation**



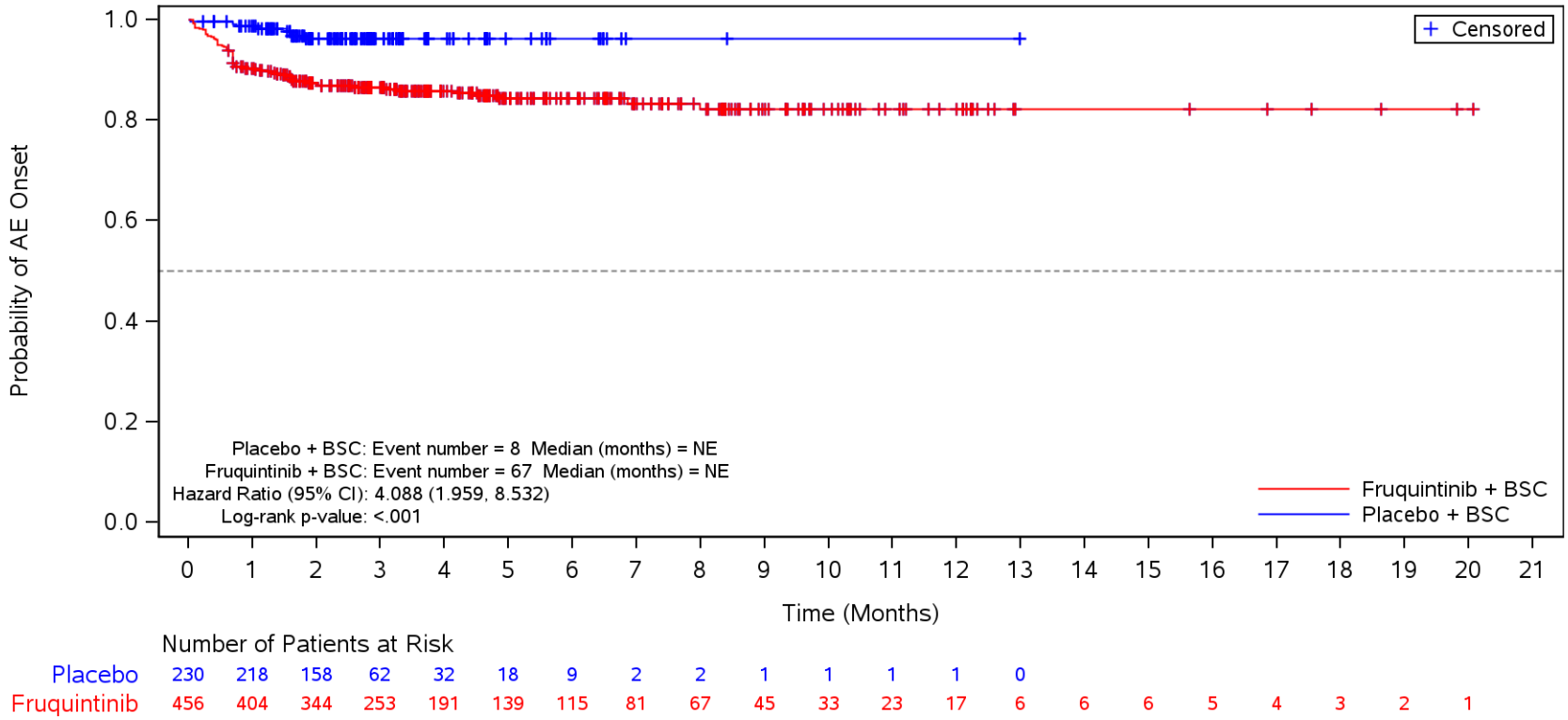
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Vomiting**



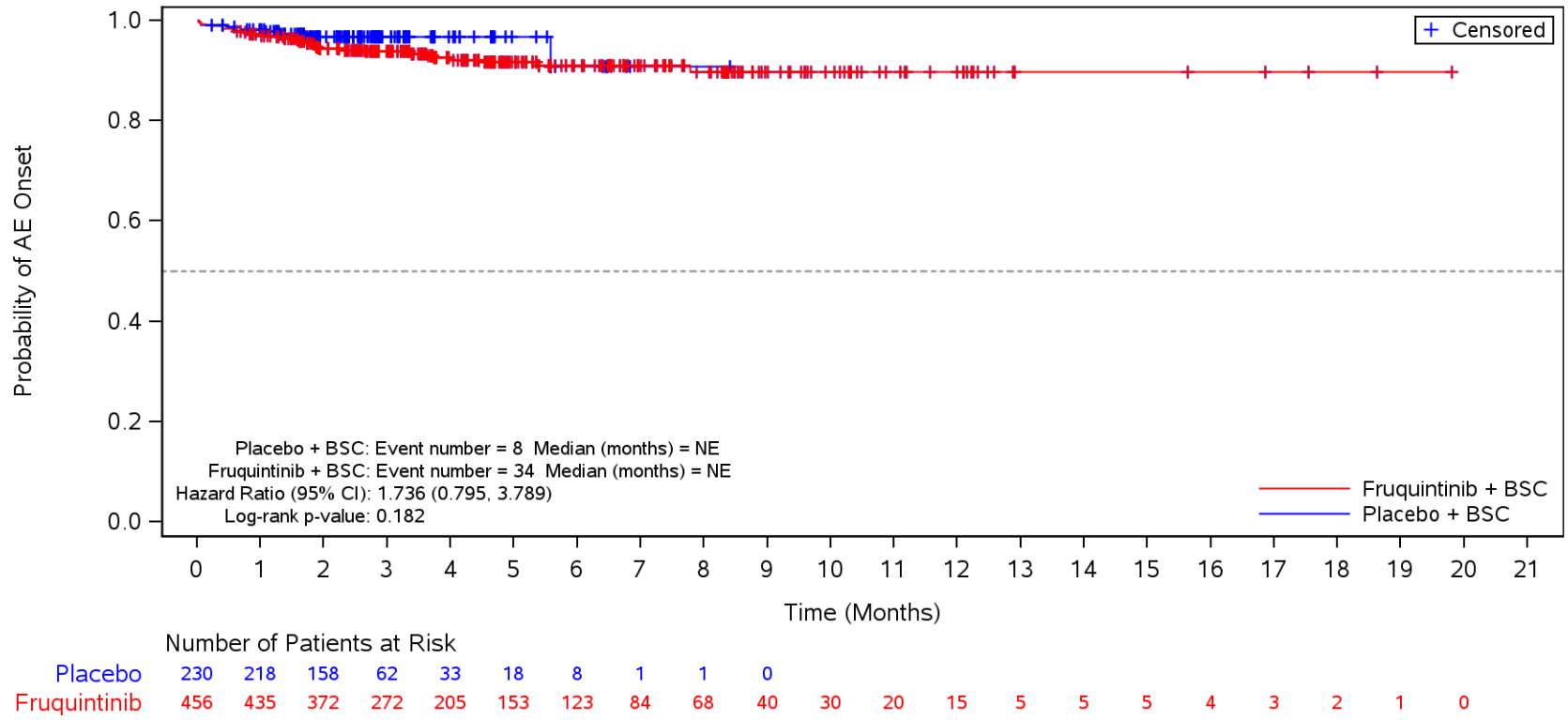
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Stomatitis**



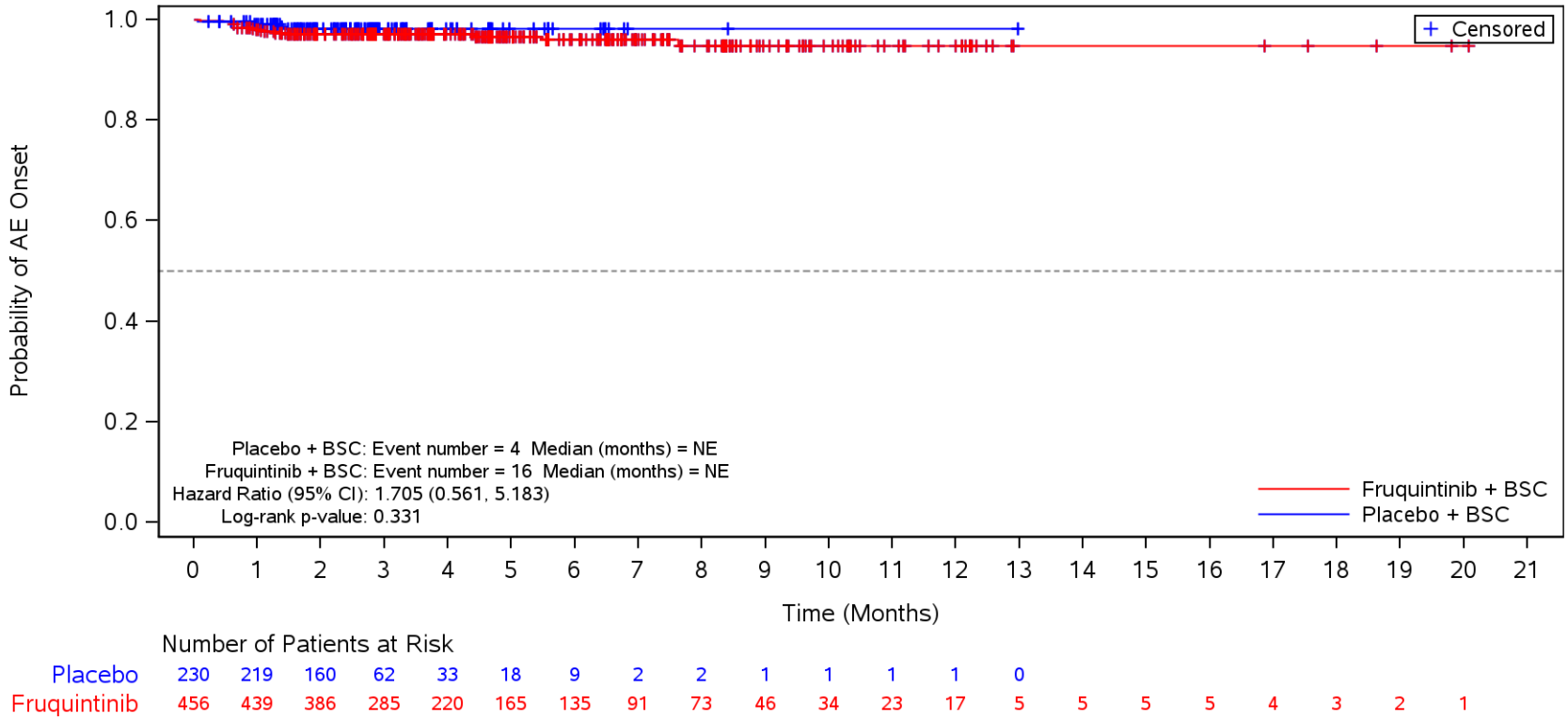
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Abdominal pain upper**



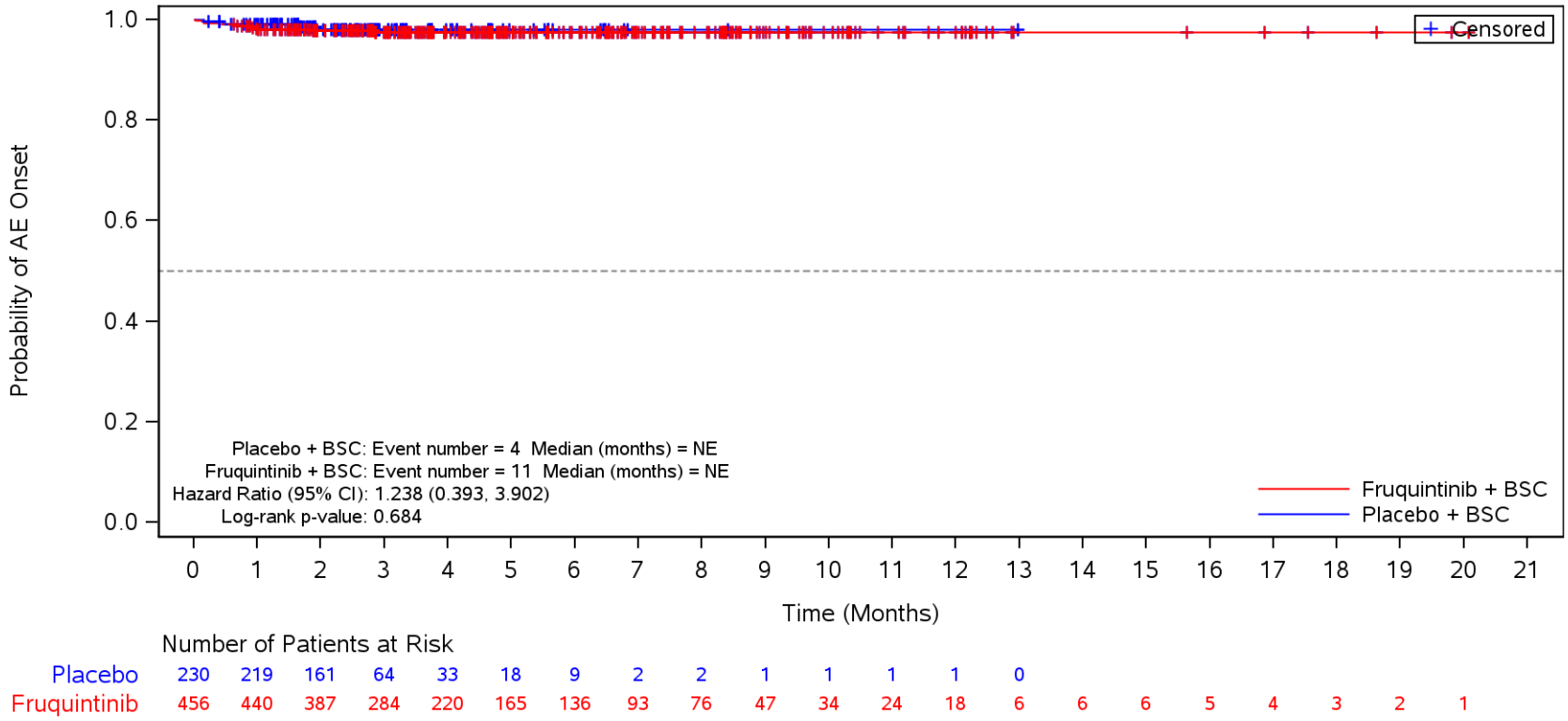
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Proctalgia**



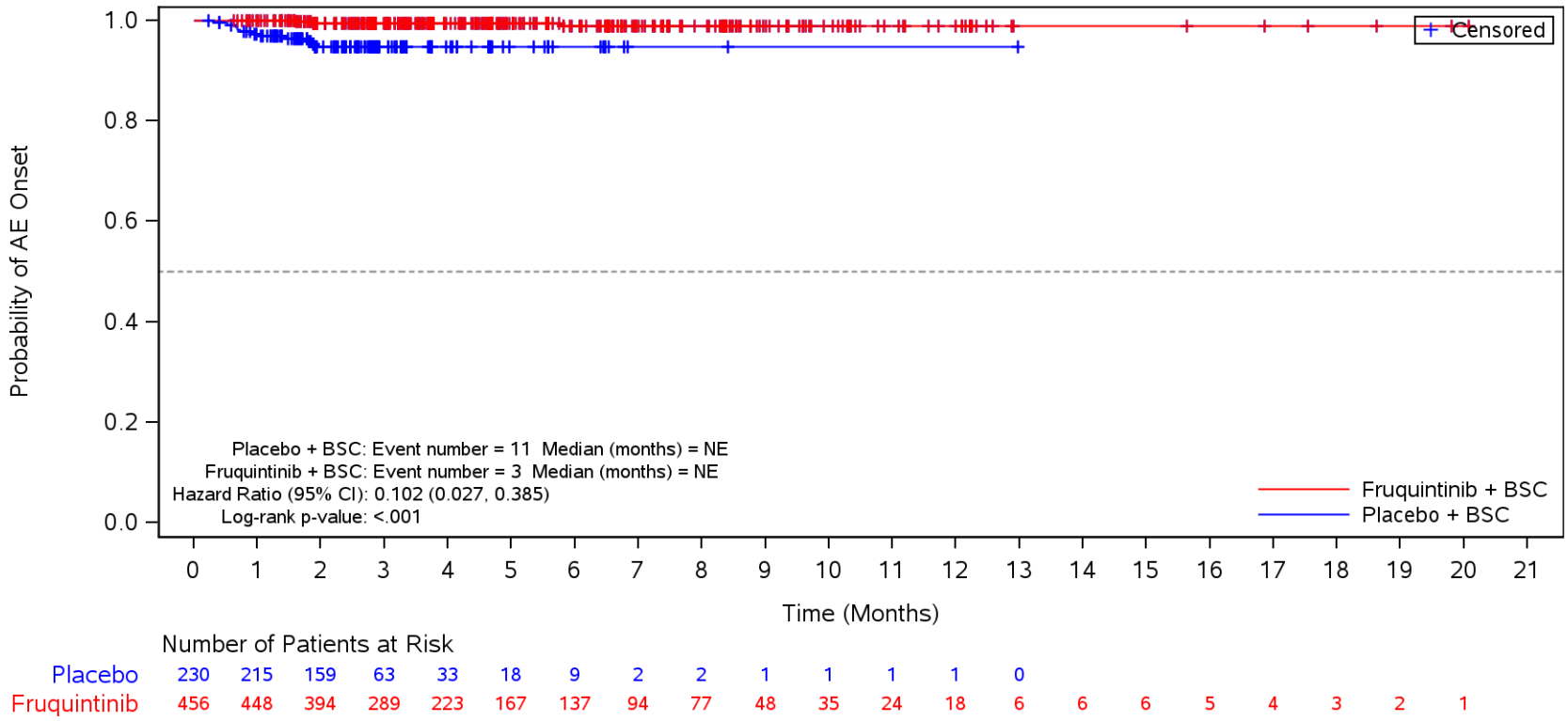
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dry mouth**



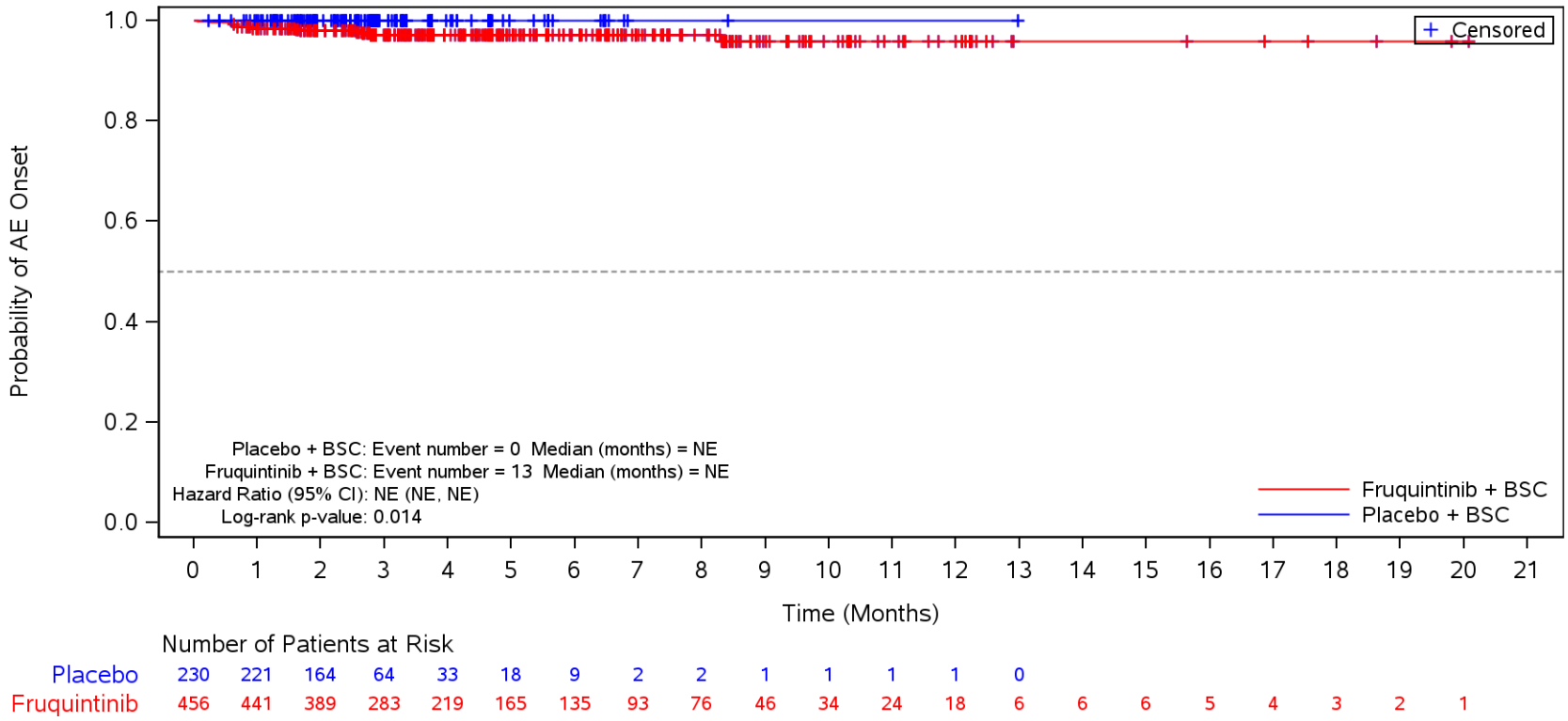
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Ascites**



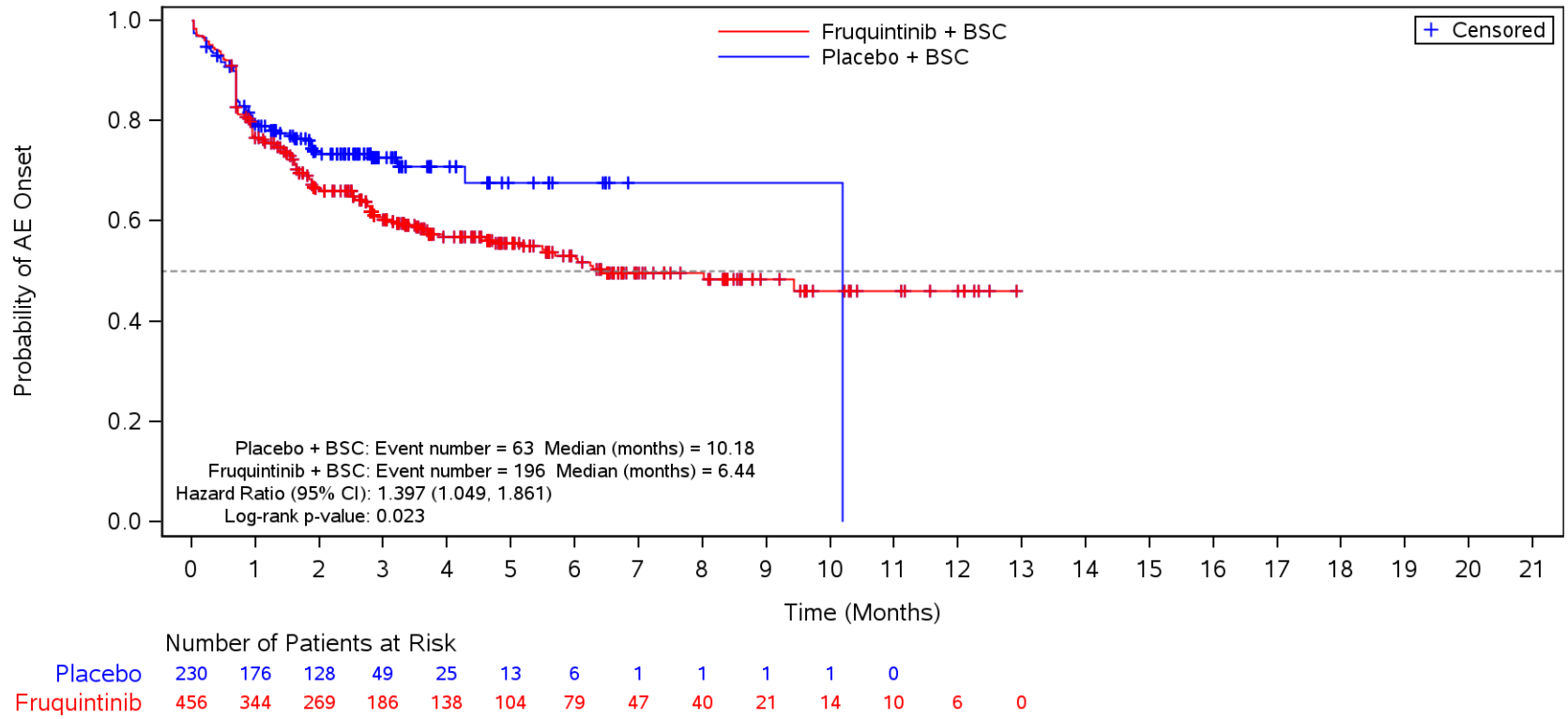
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Gastrointestinal disorders** and Preferred Term **Dyspepsia**



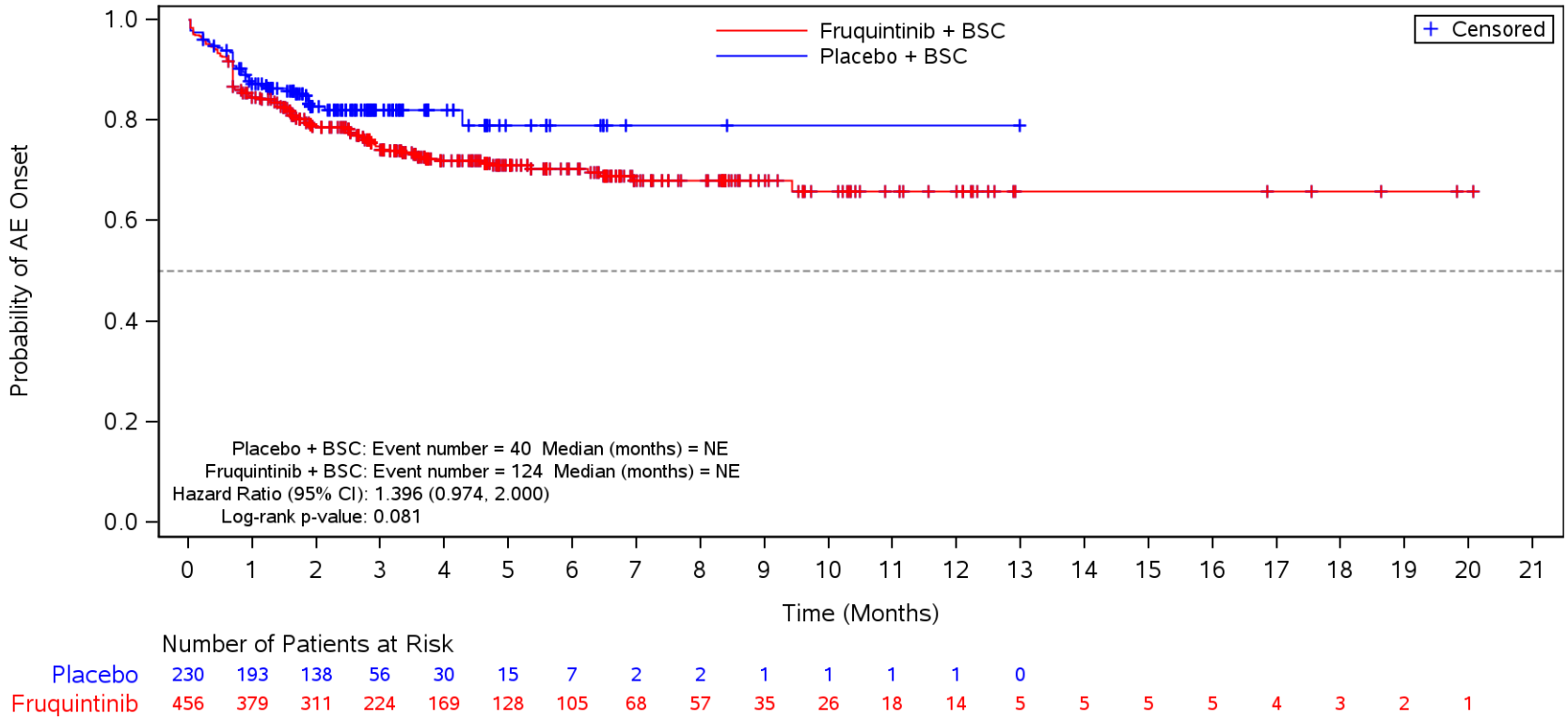
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders**



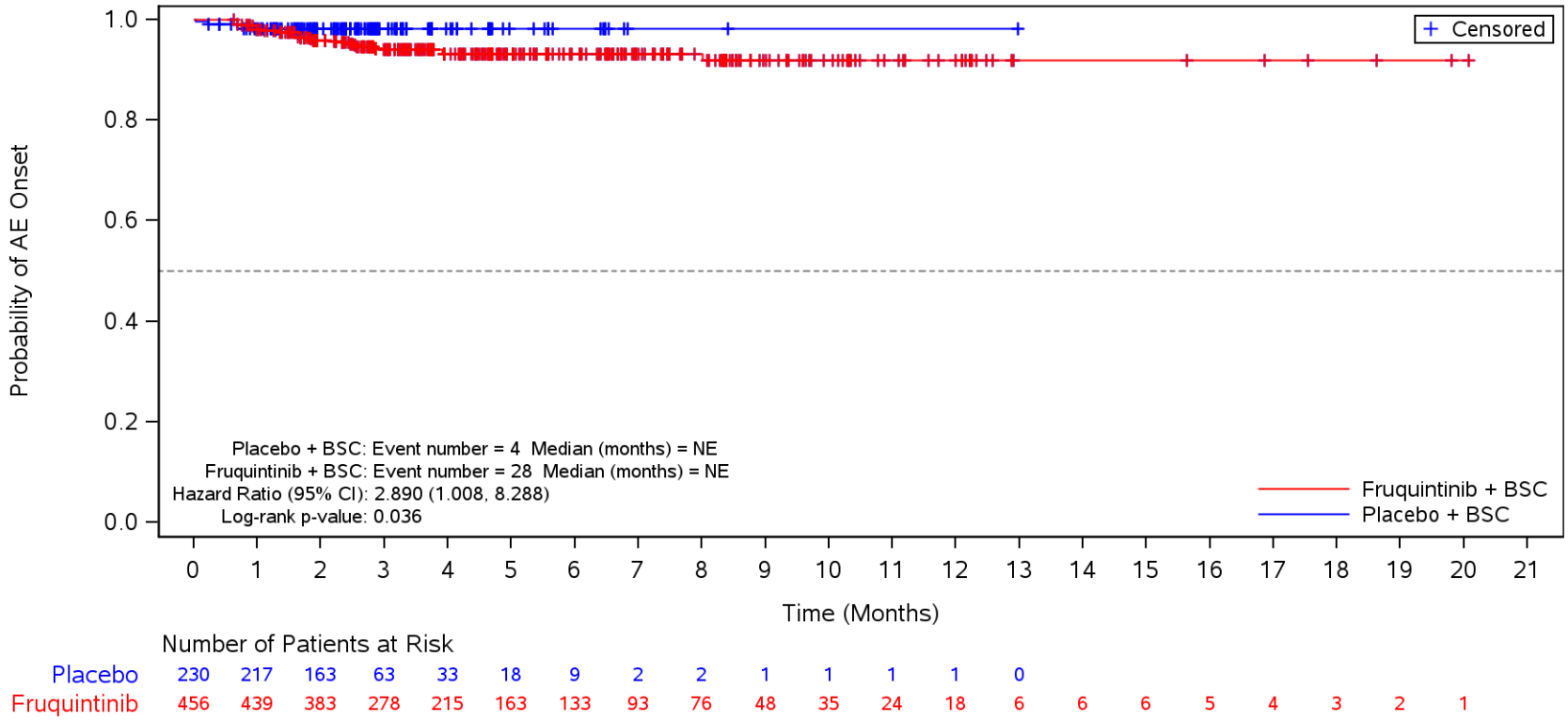
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Decreased appetite**



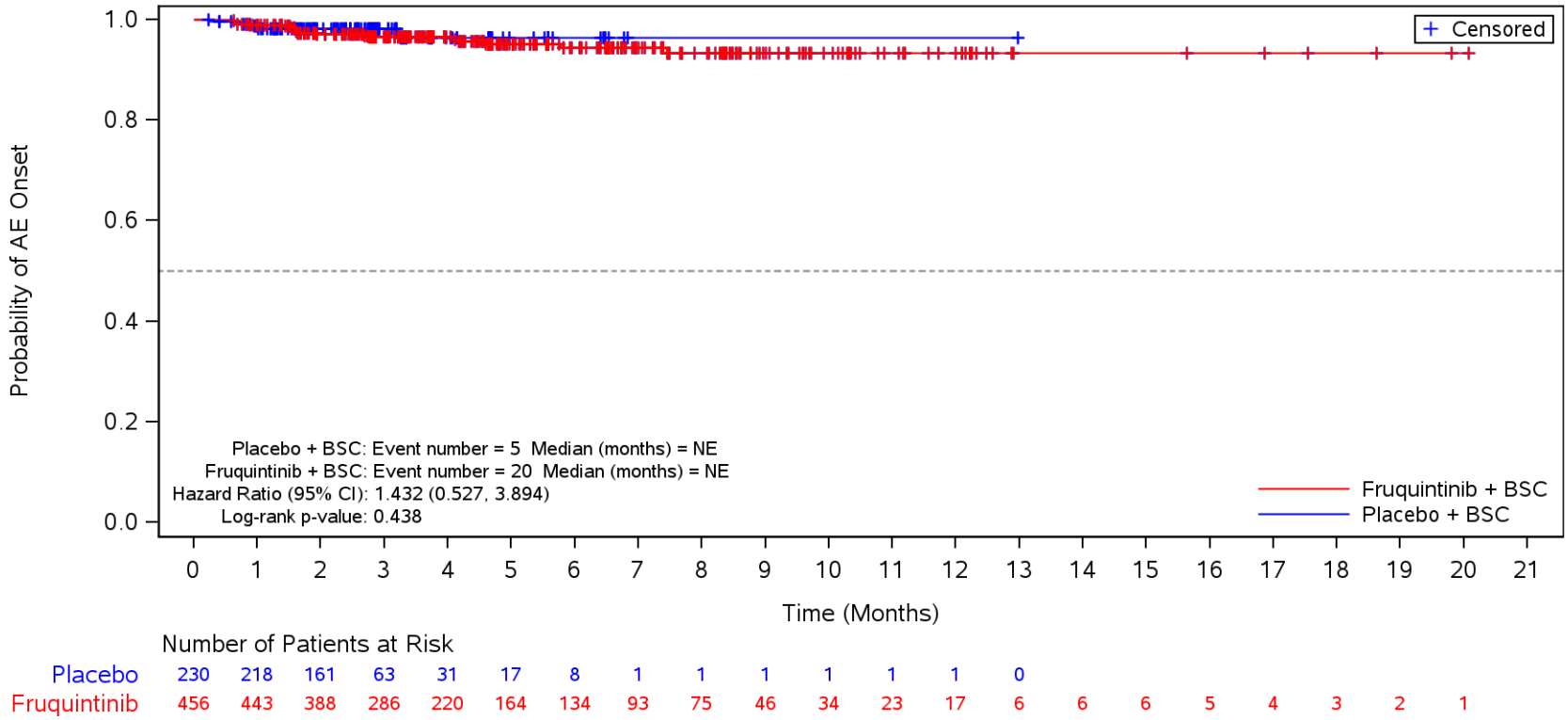
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypokalaemia**



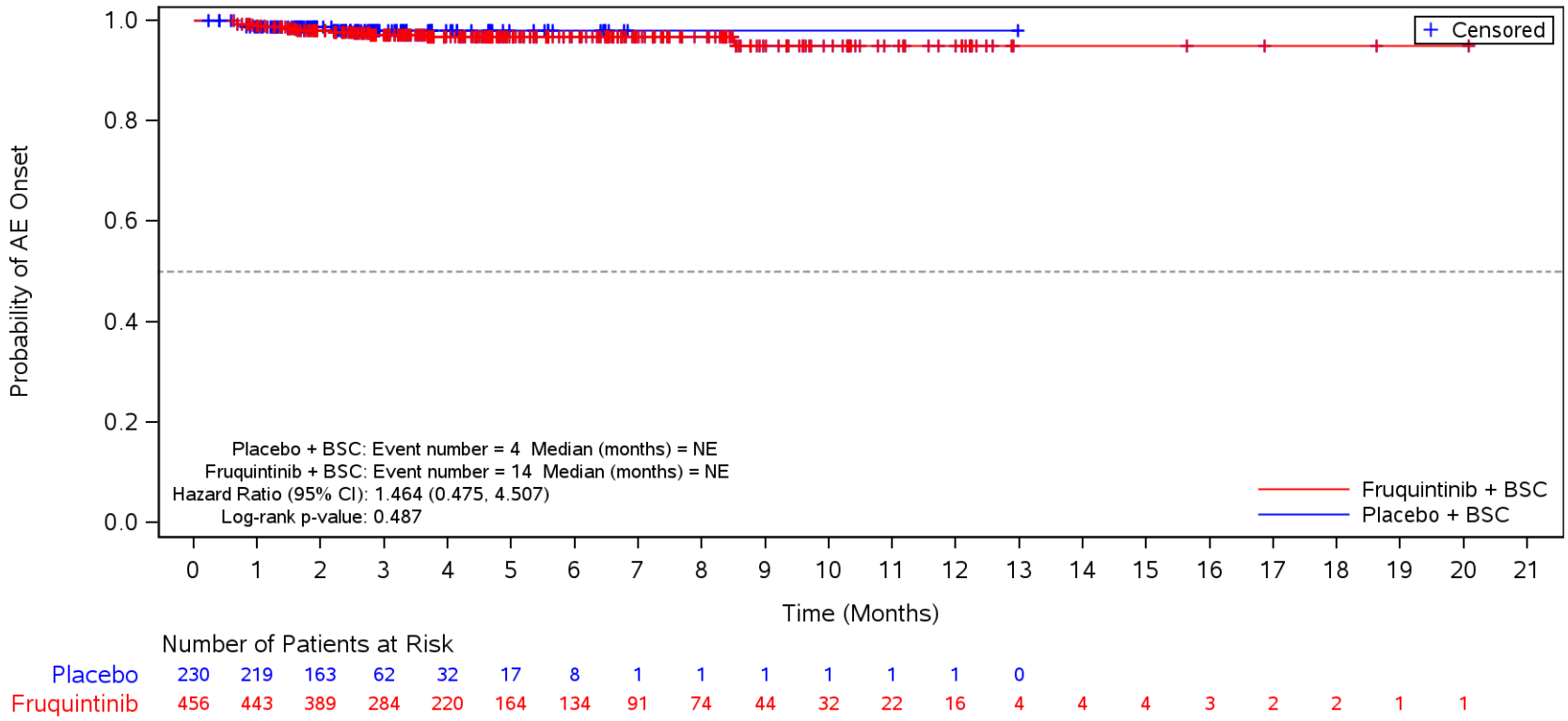
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyponatraemia**



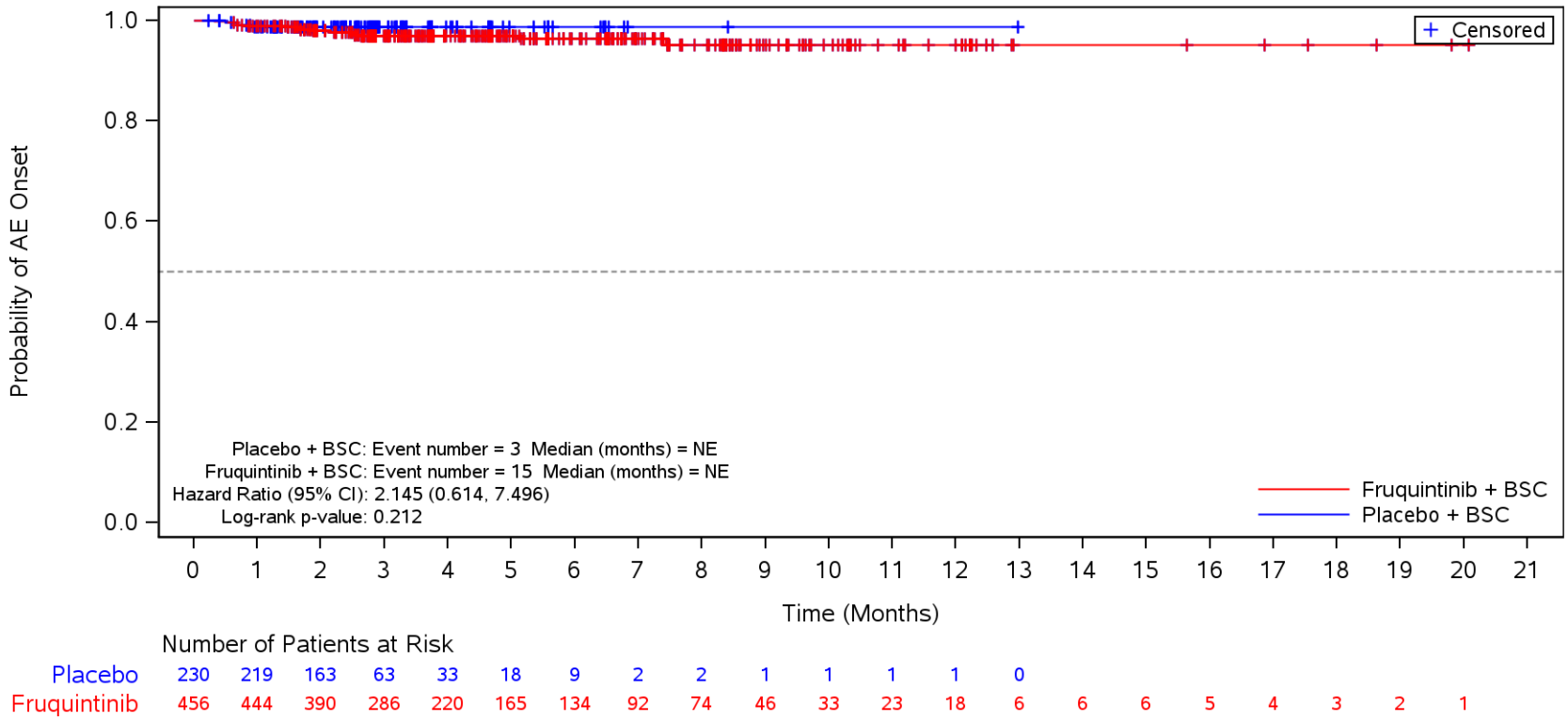
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperuricaemia**



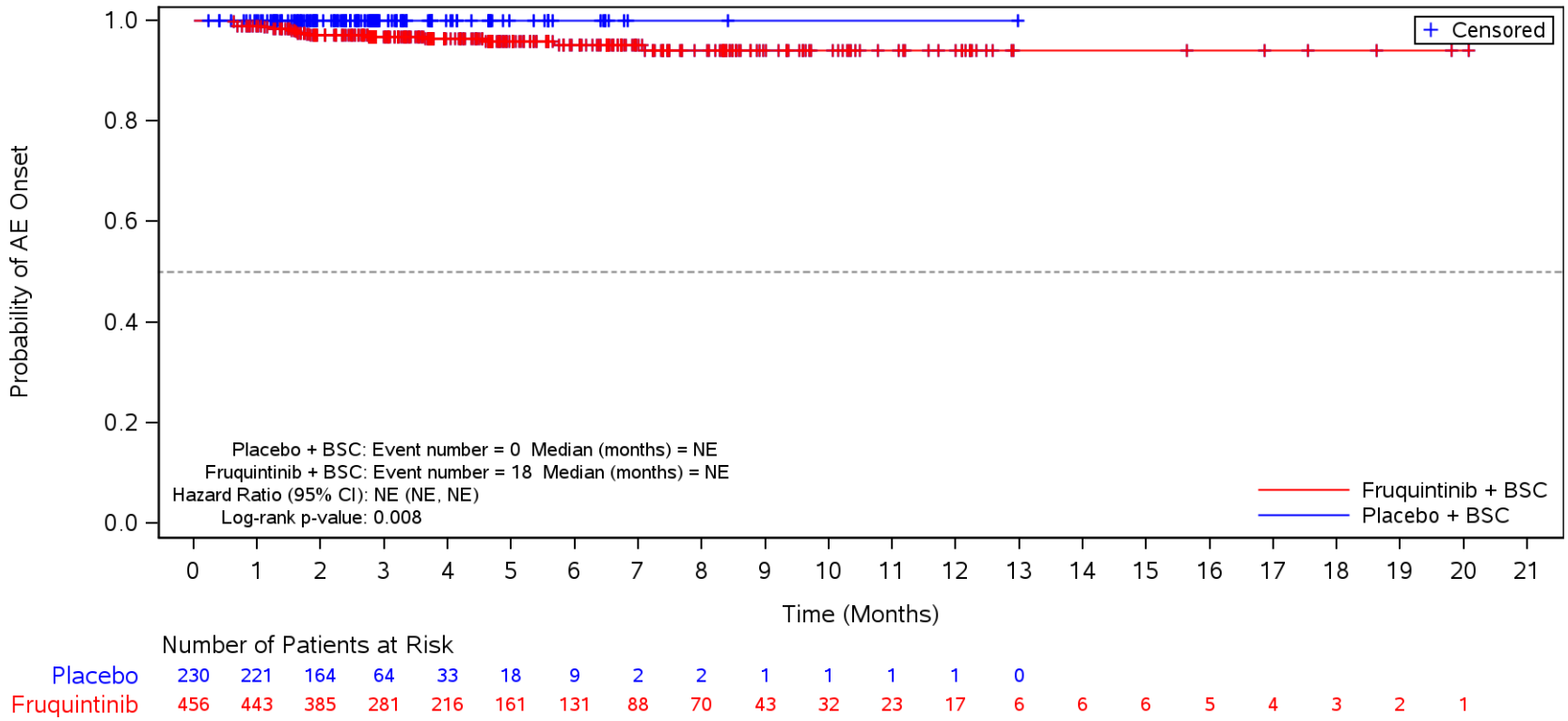
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypoalbuminaemia**



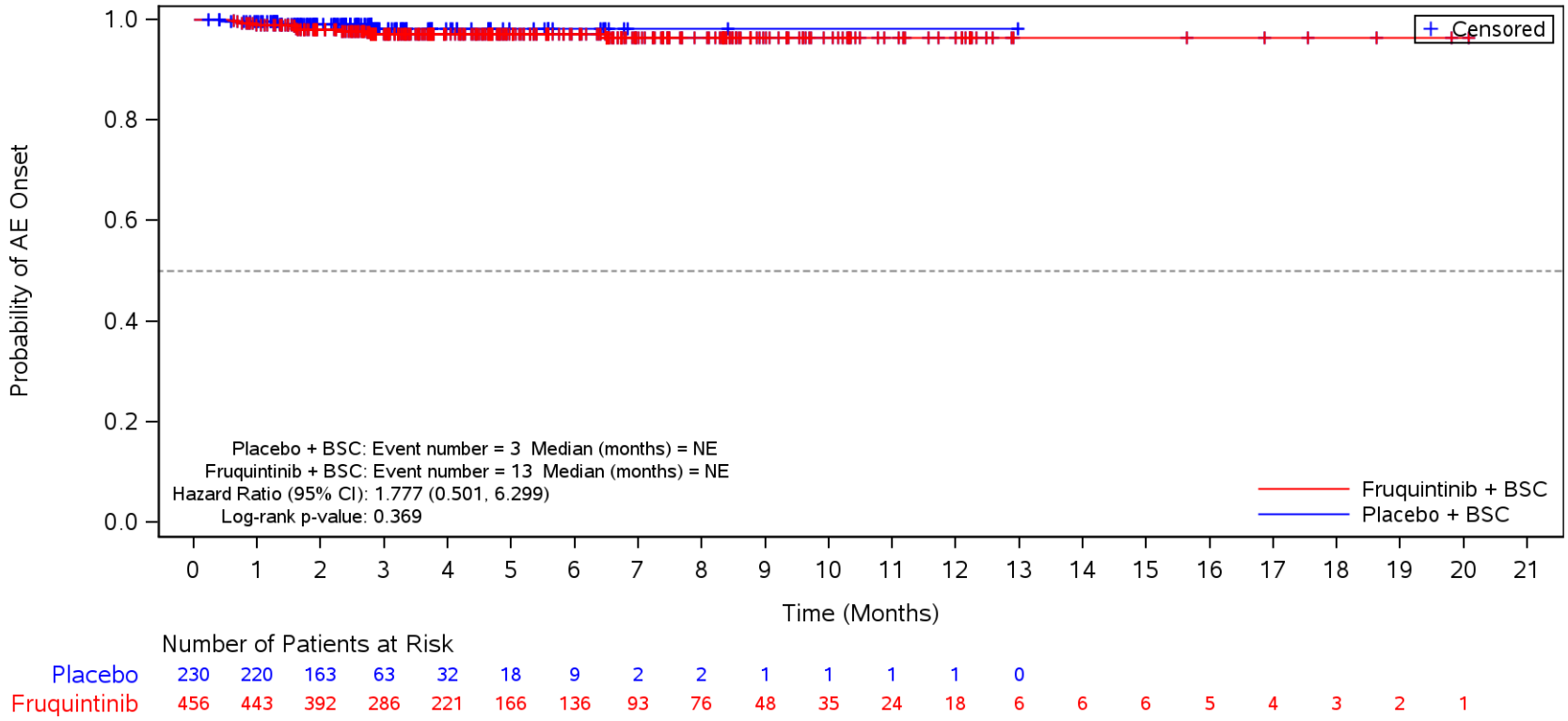
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypomagnesaemia**



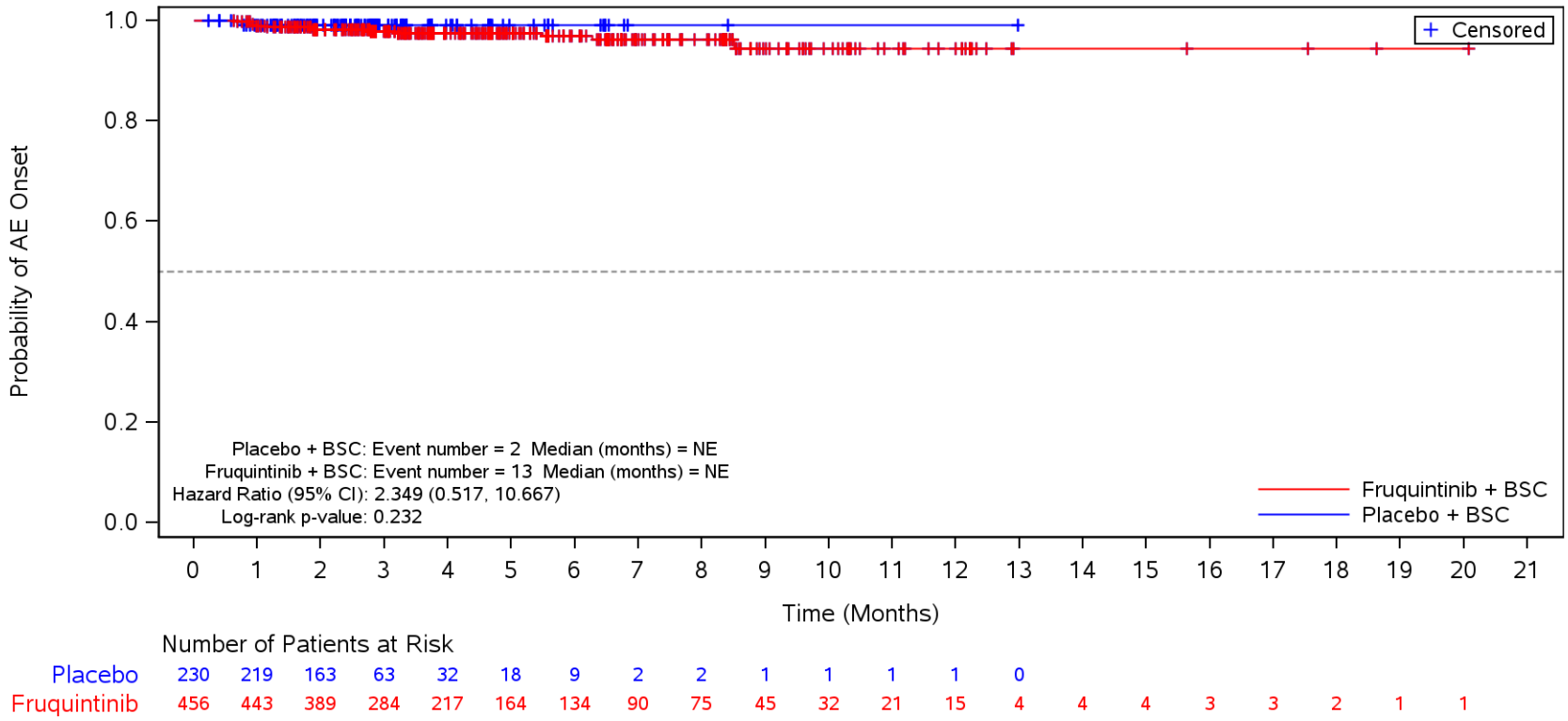
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Dehydration**



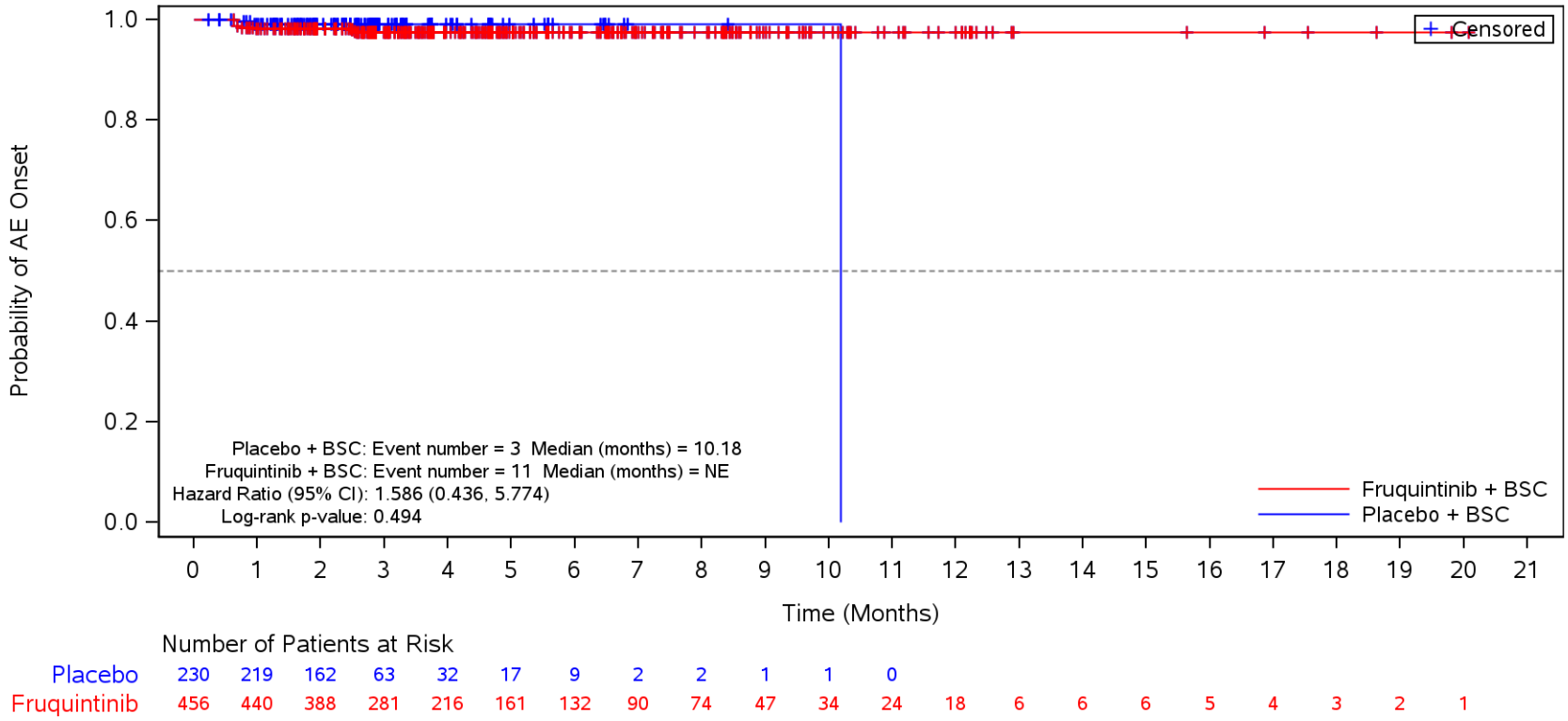
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hyperglycaemia**



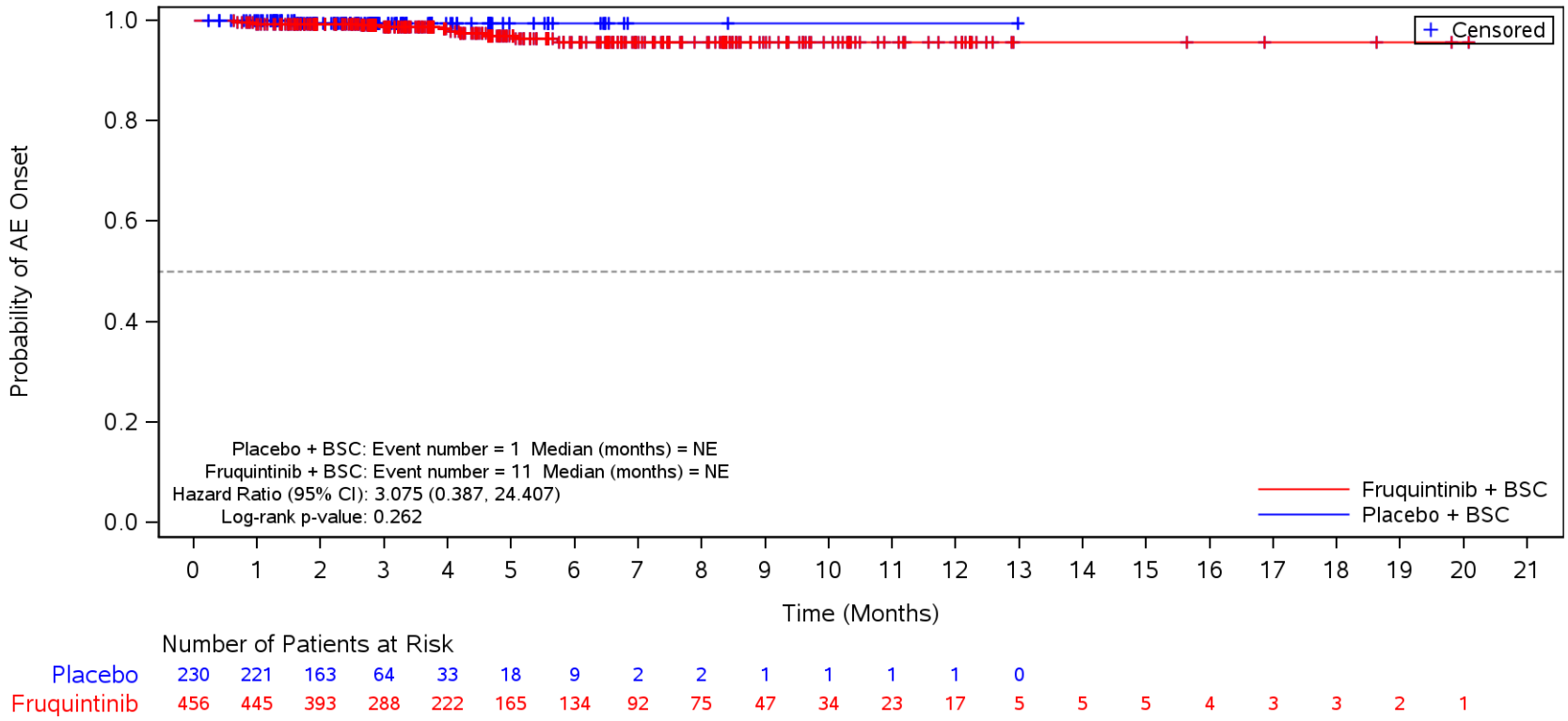
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypertriglyceridaemia**



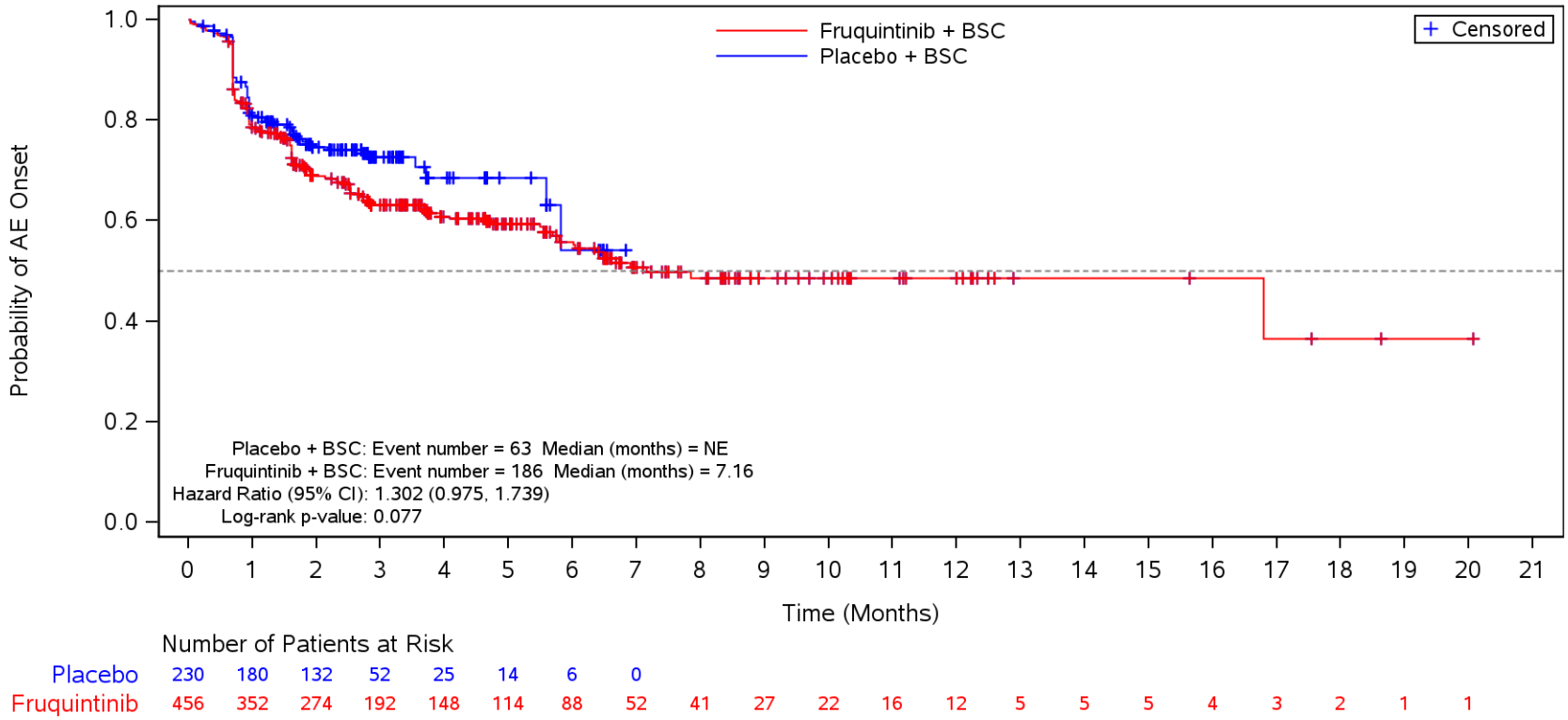
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Metabolism and nutrition disorders** and Preferred Term **Hypophosphataemia**



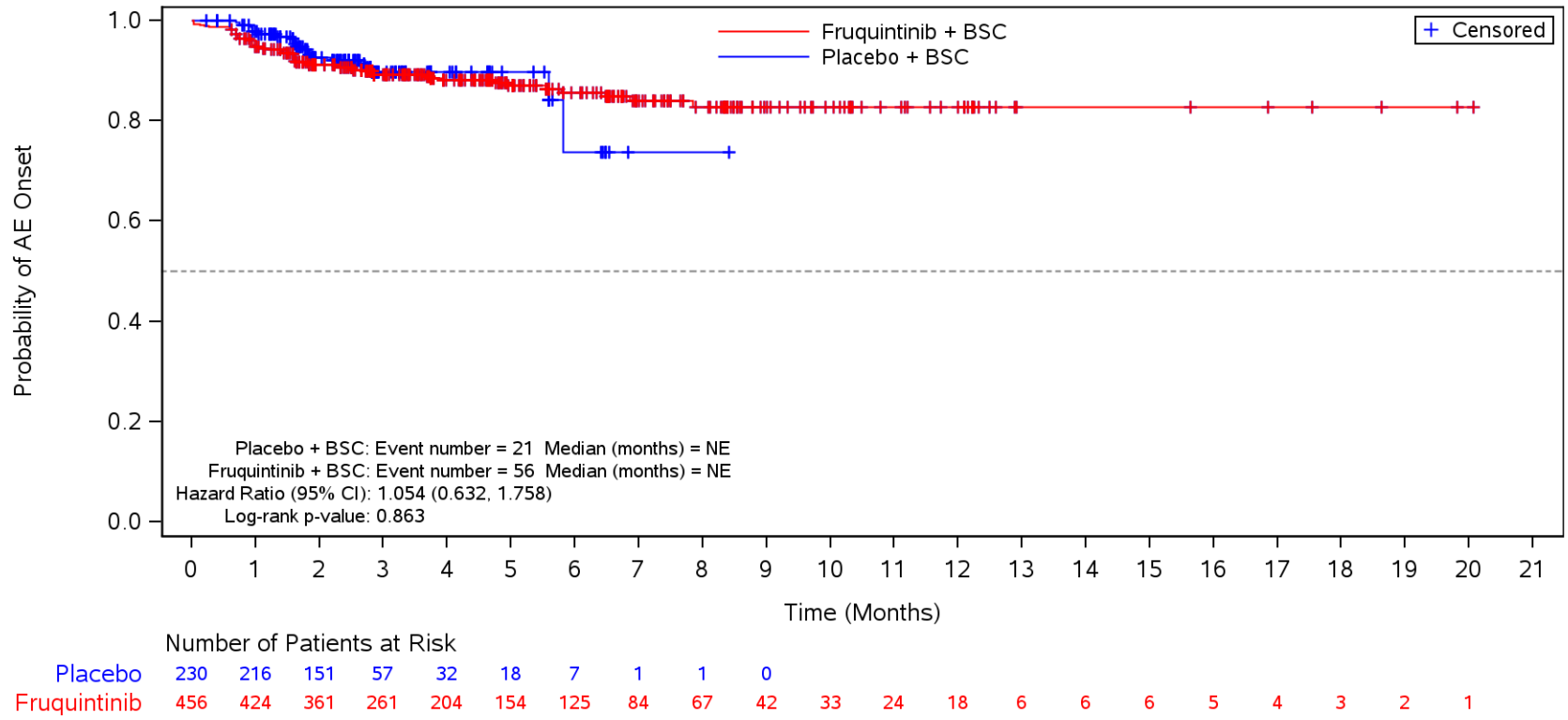
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations**



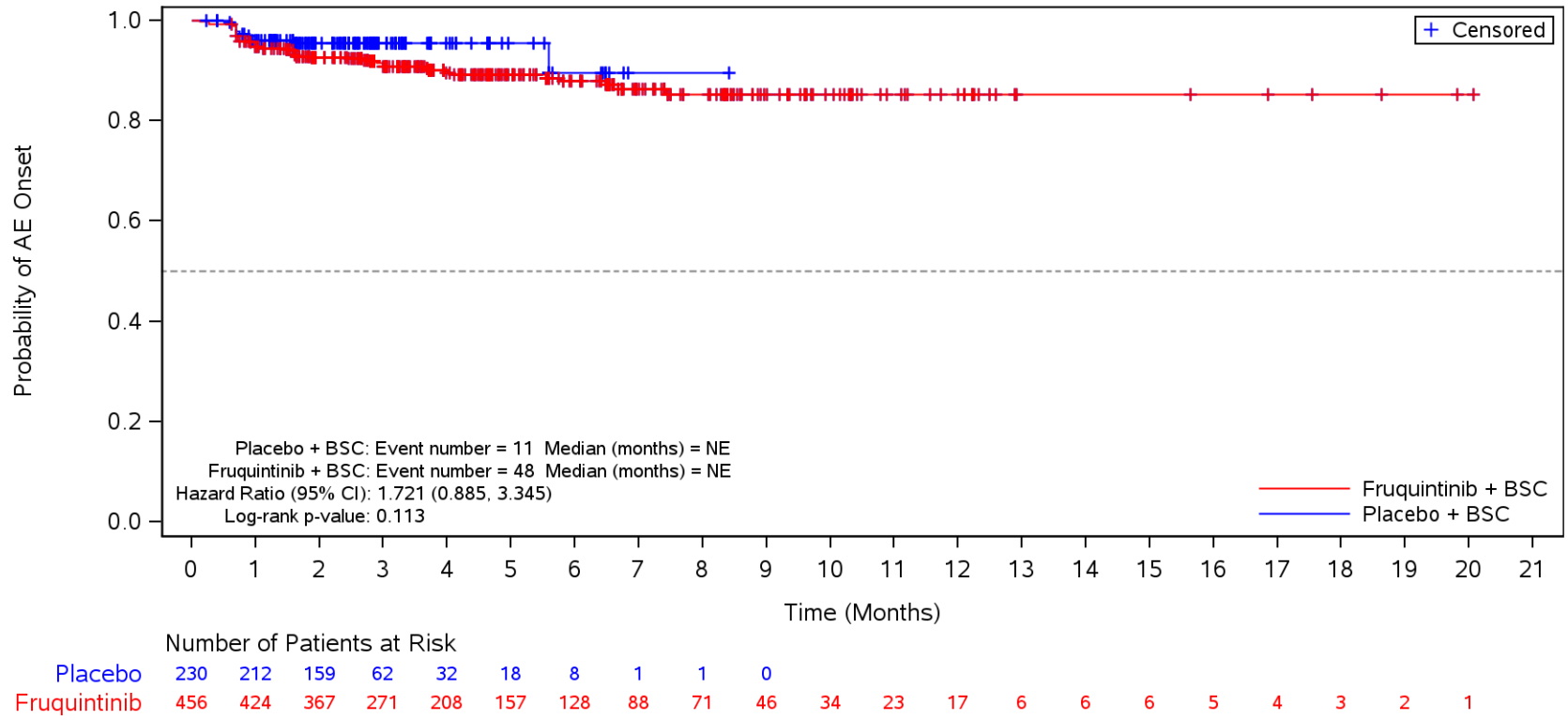
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Weight decreased**



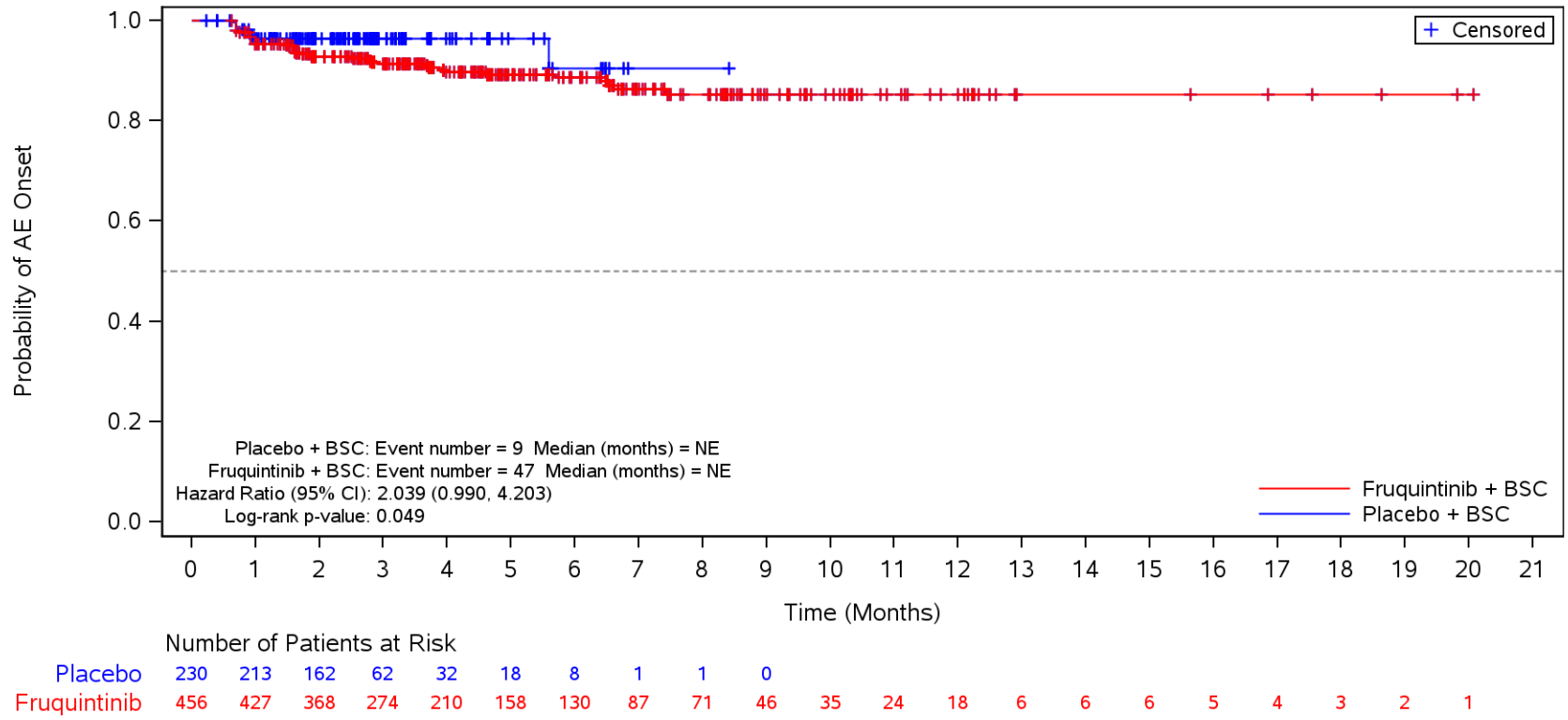
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Aspartate aminotransferase increased**



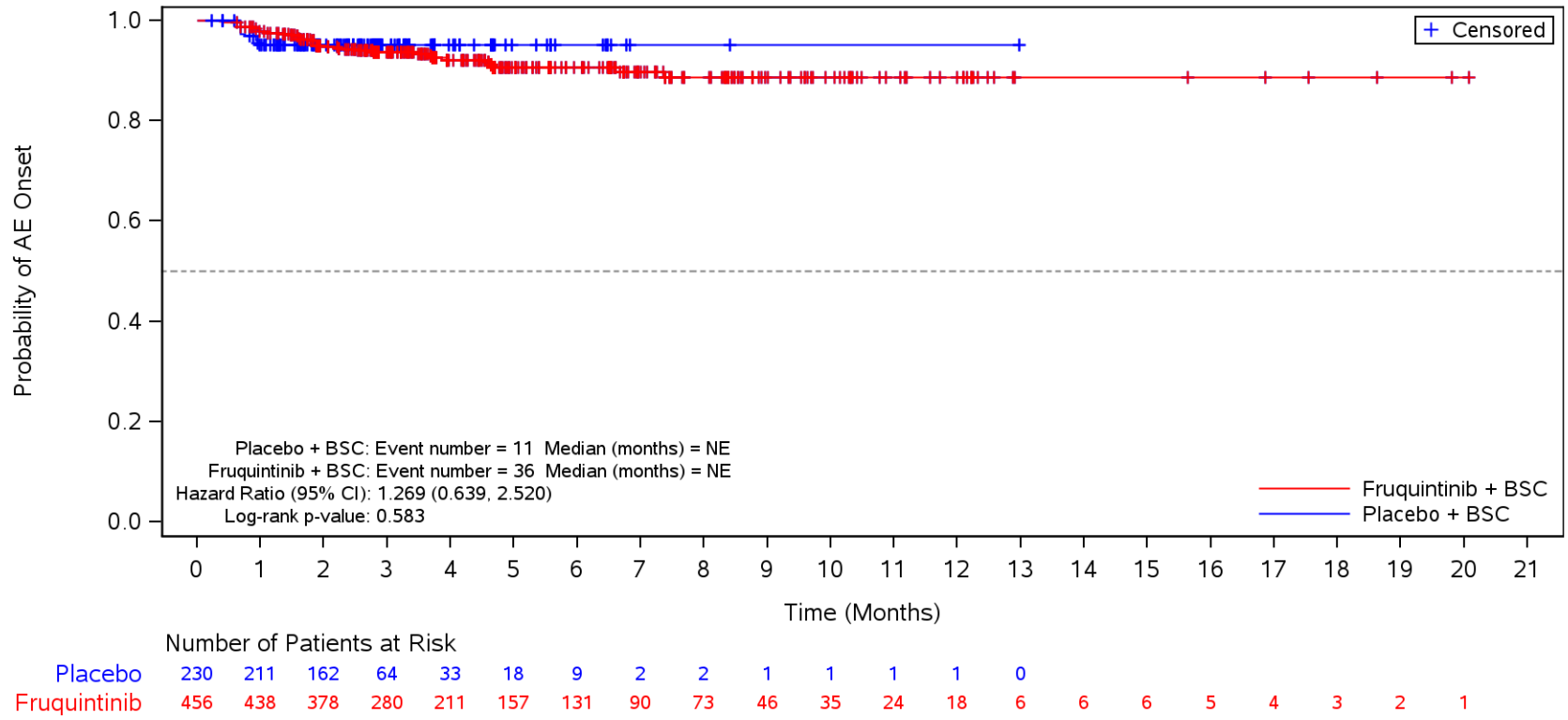
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Alanine aminotransferase increased**



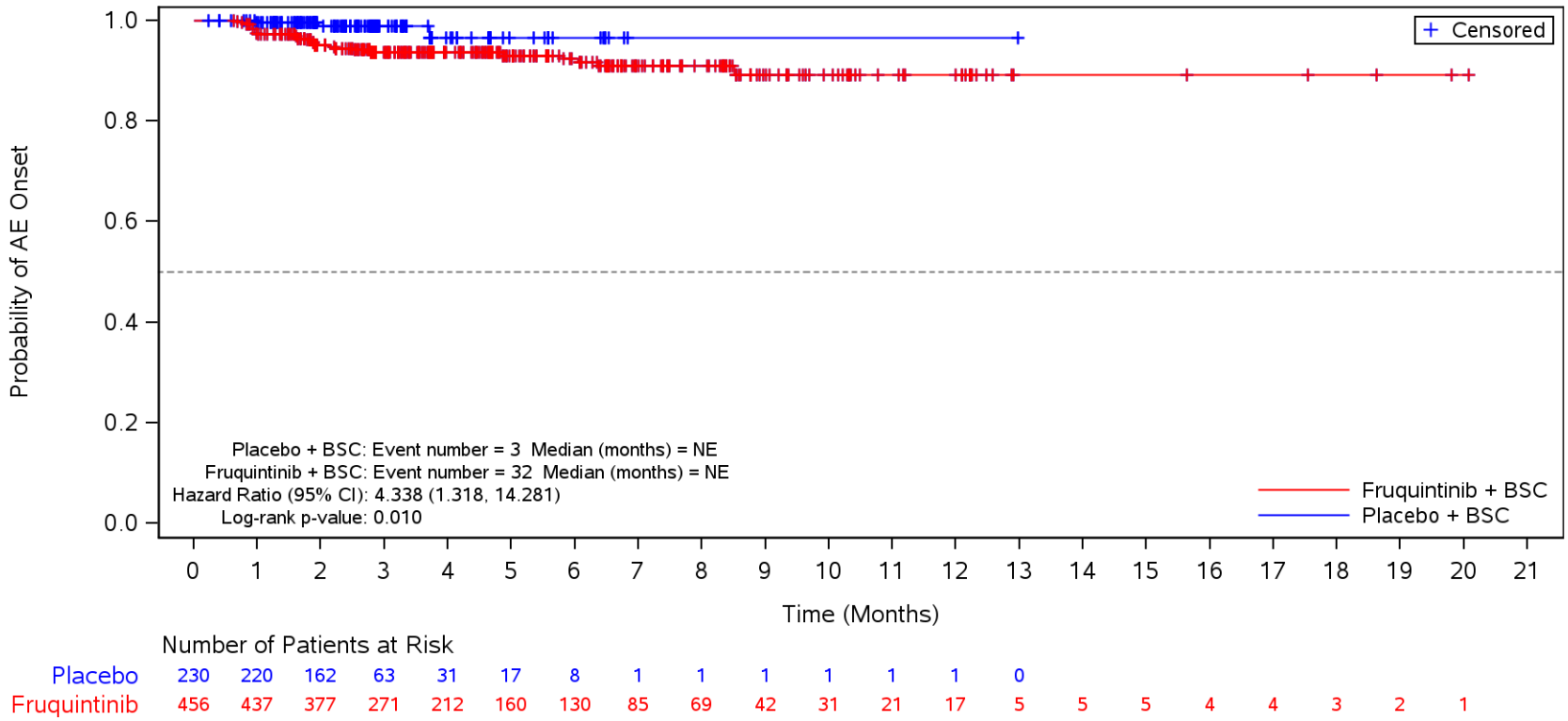
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood bilirubin increased**



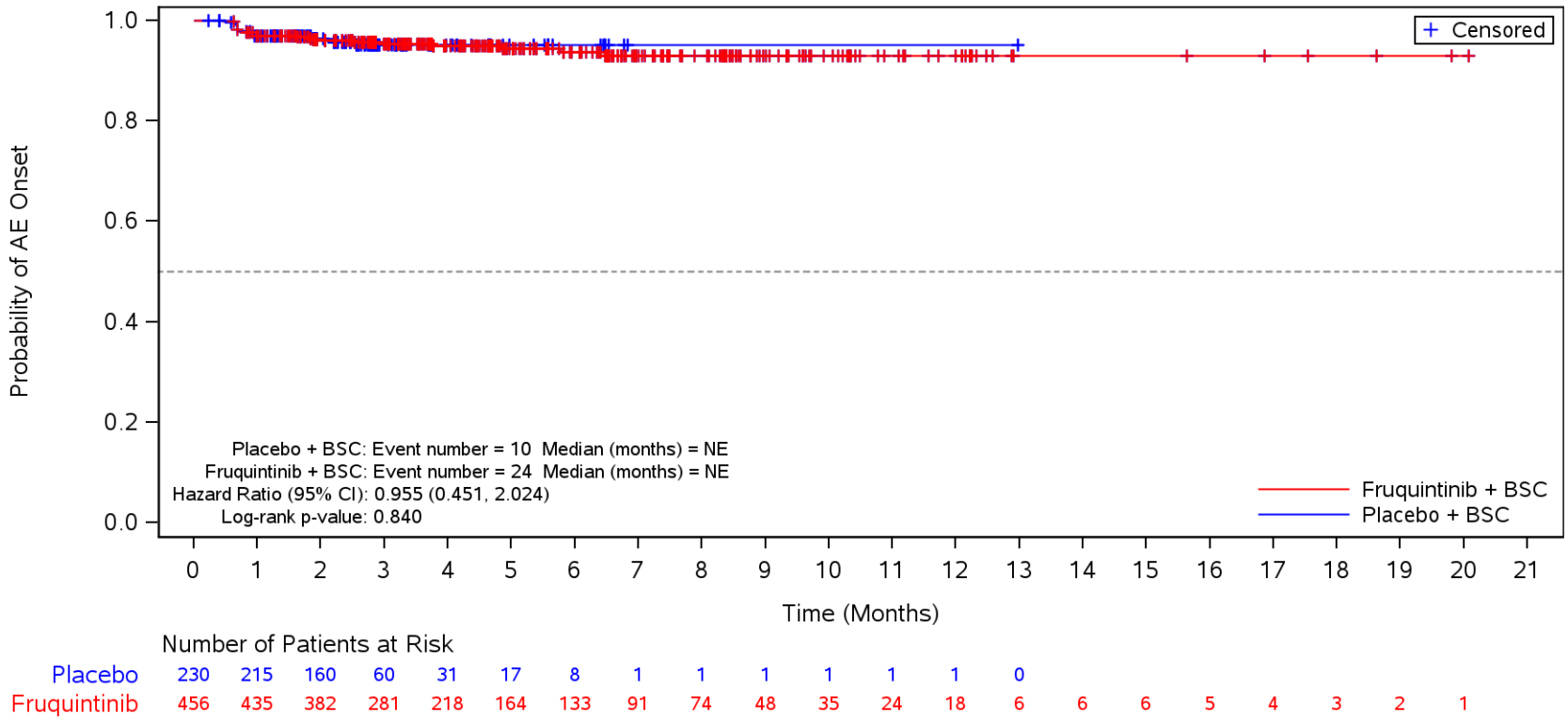
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood thyroid stimulating hormone increased**



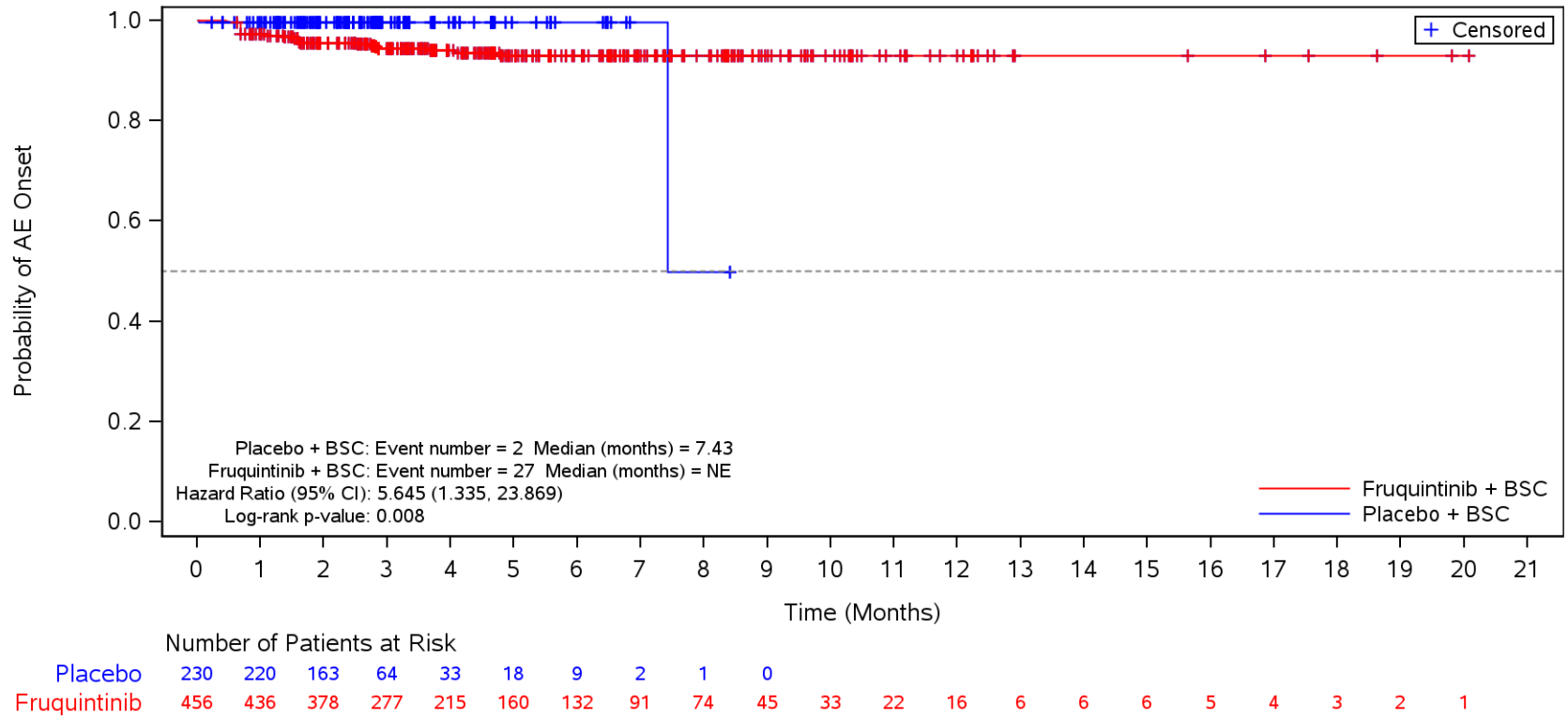
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood alkaline phosphatase increased**



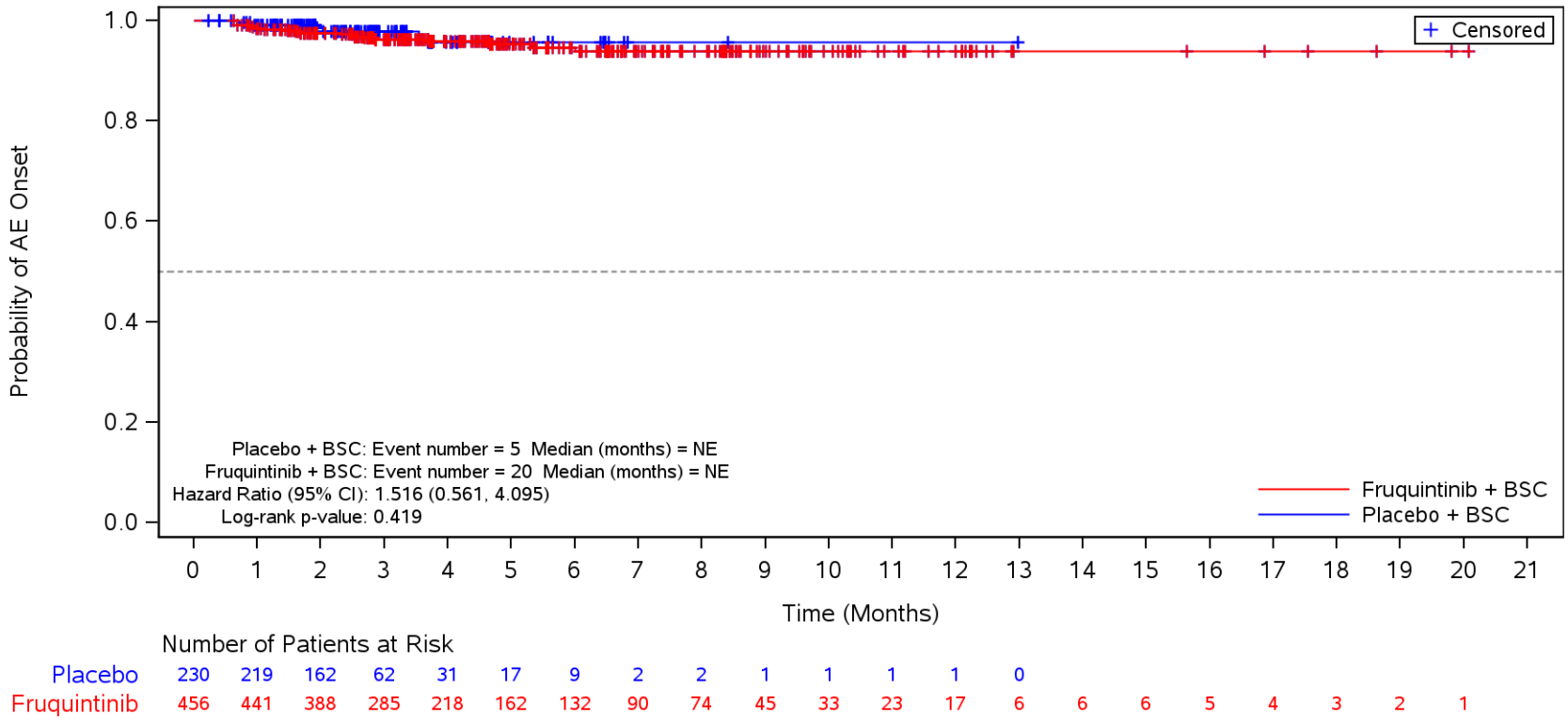
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Platelet count decreased**



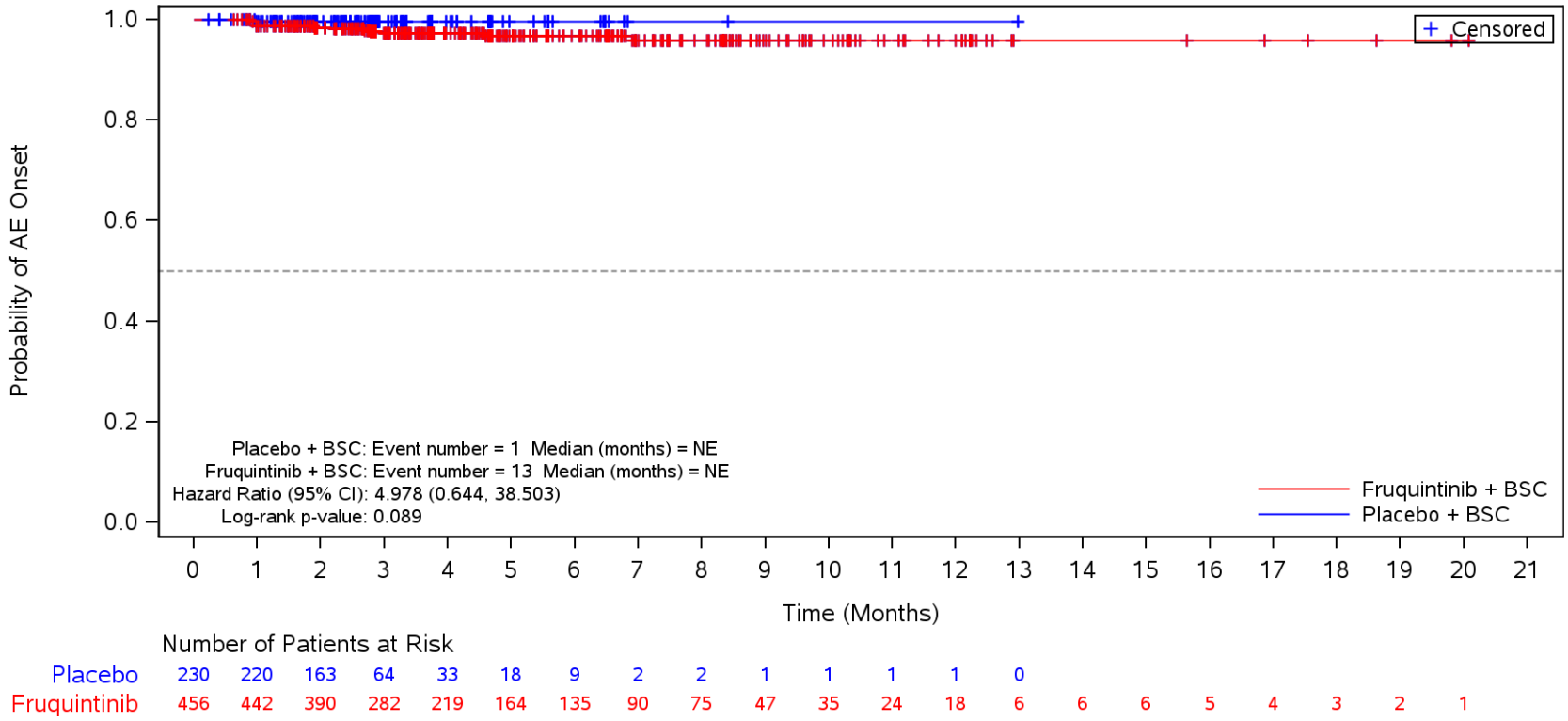
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Blood creatinine increased**



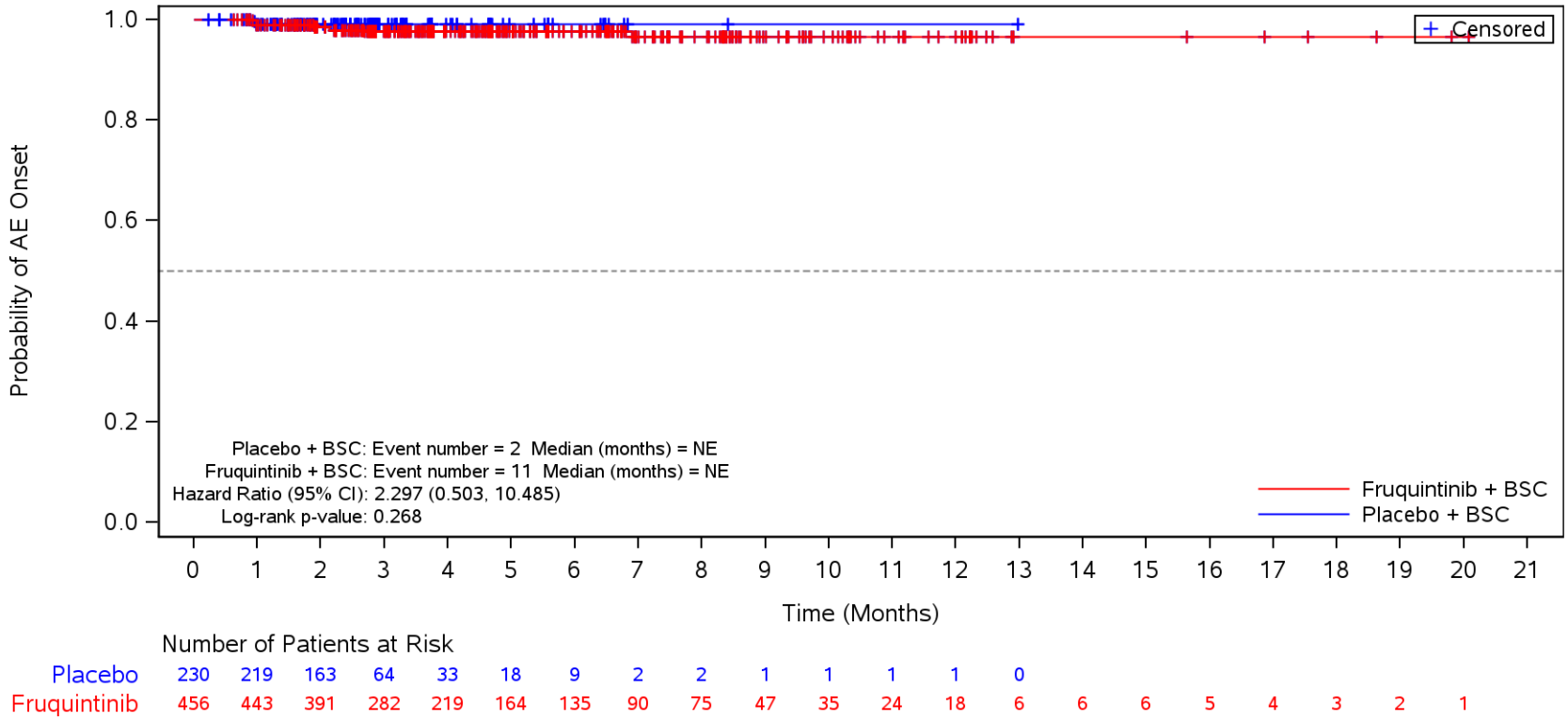
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Amylase increased**



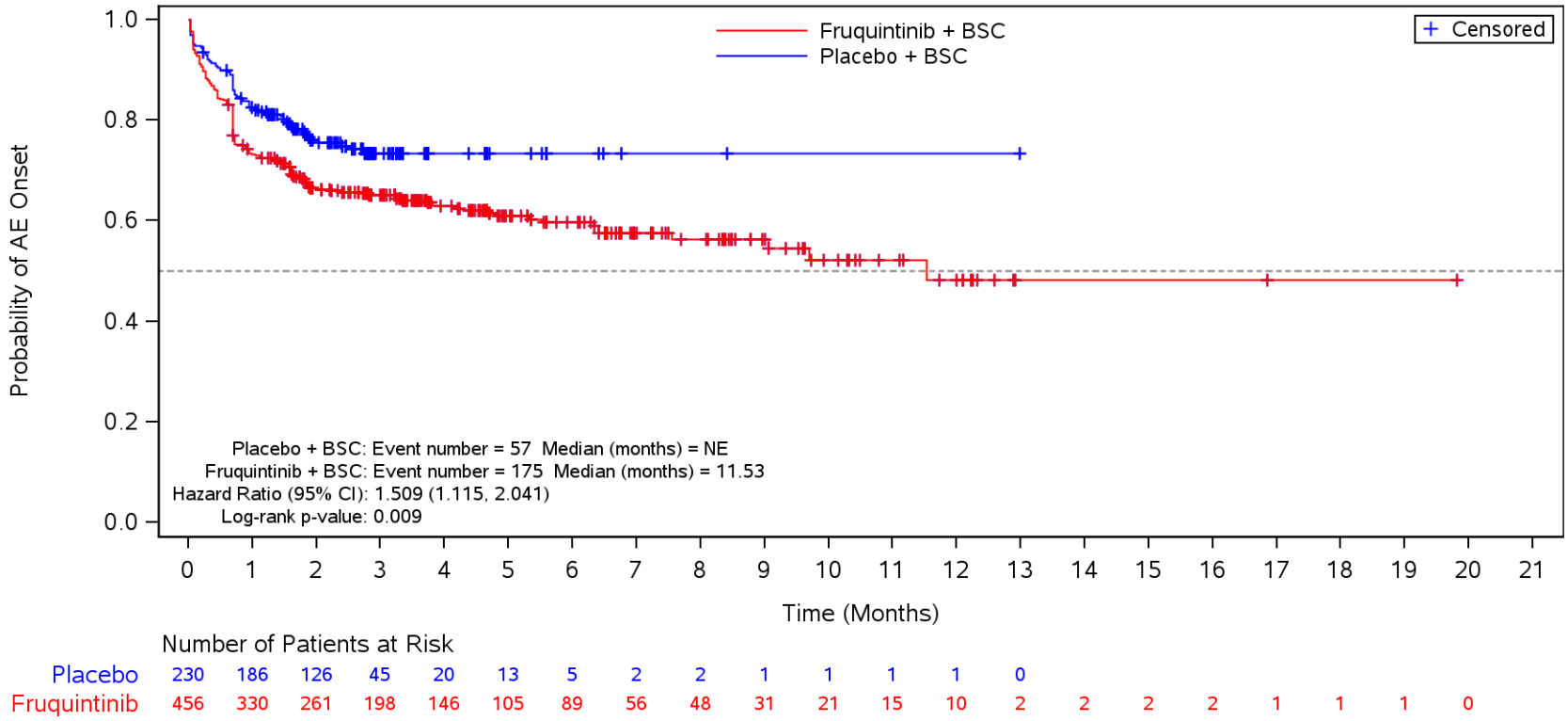
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Investigations** and Preferred Term **Lipase increased**



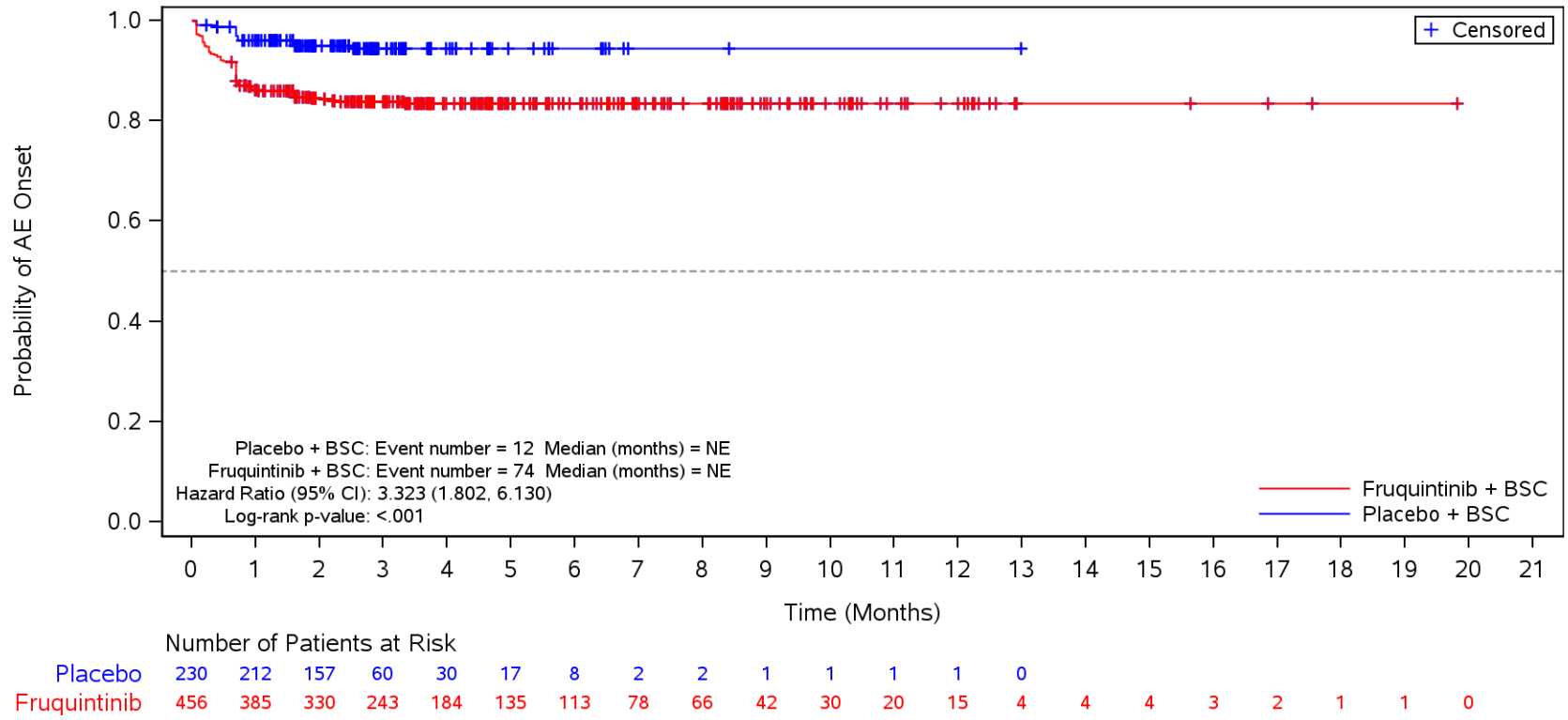
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders**



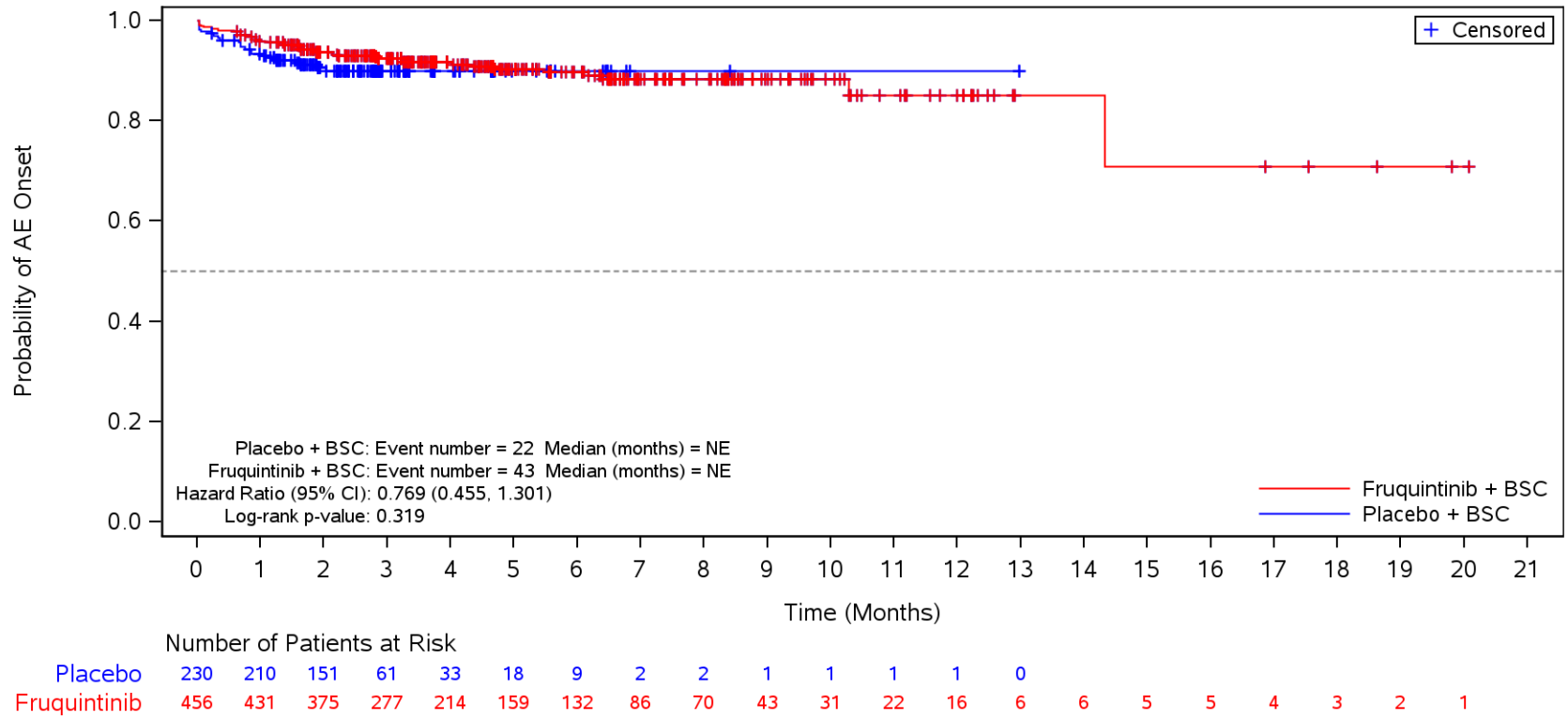
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dysphonia**



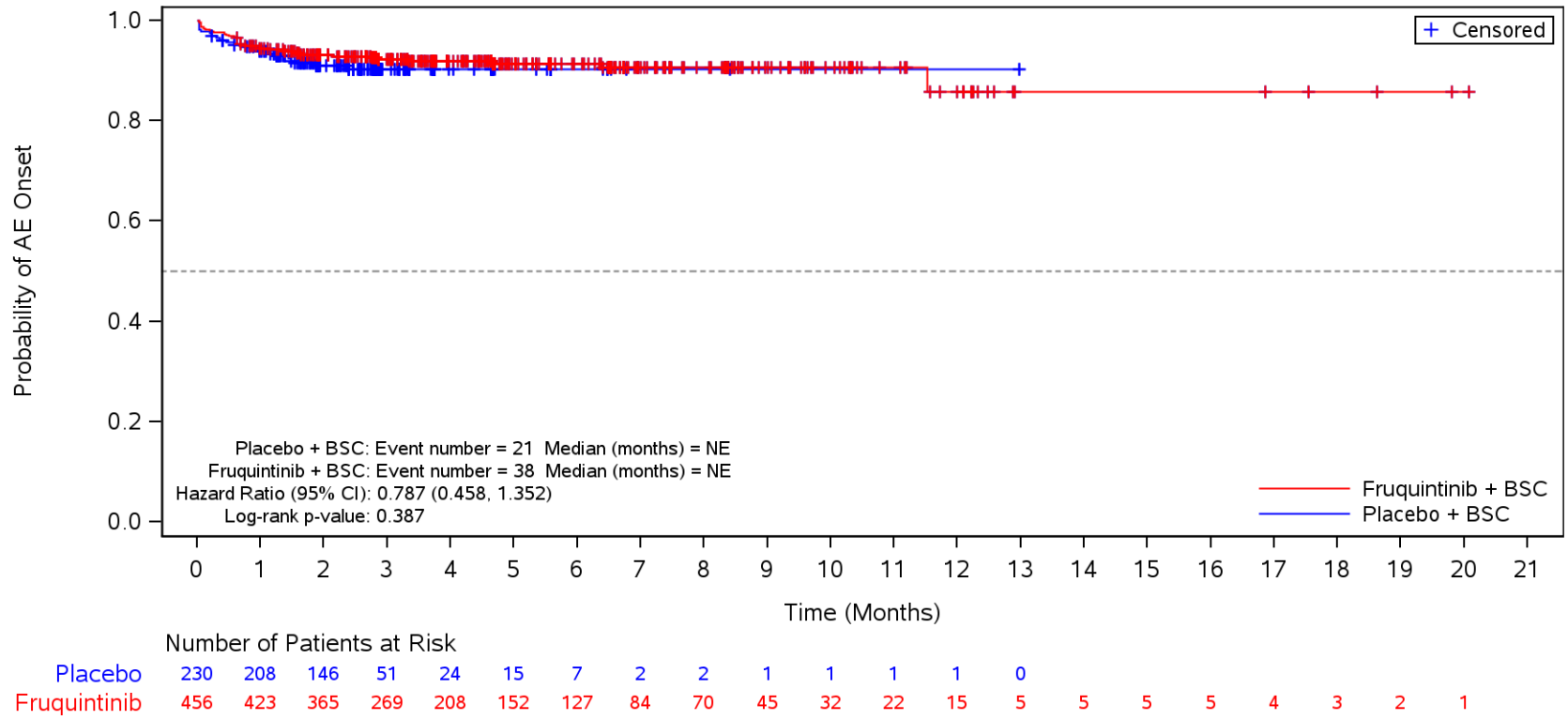
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Dyspnoea**



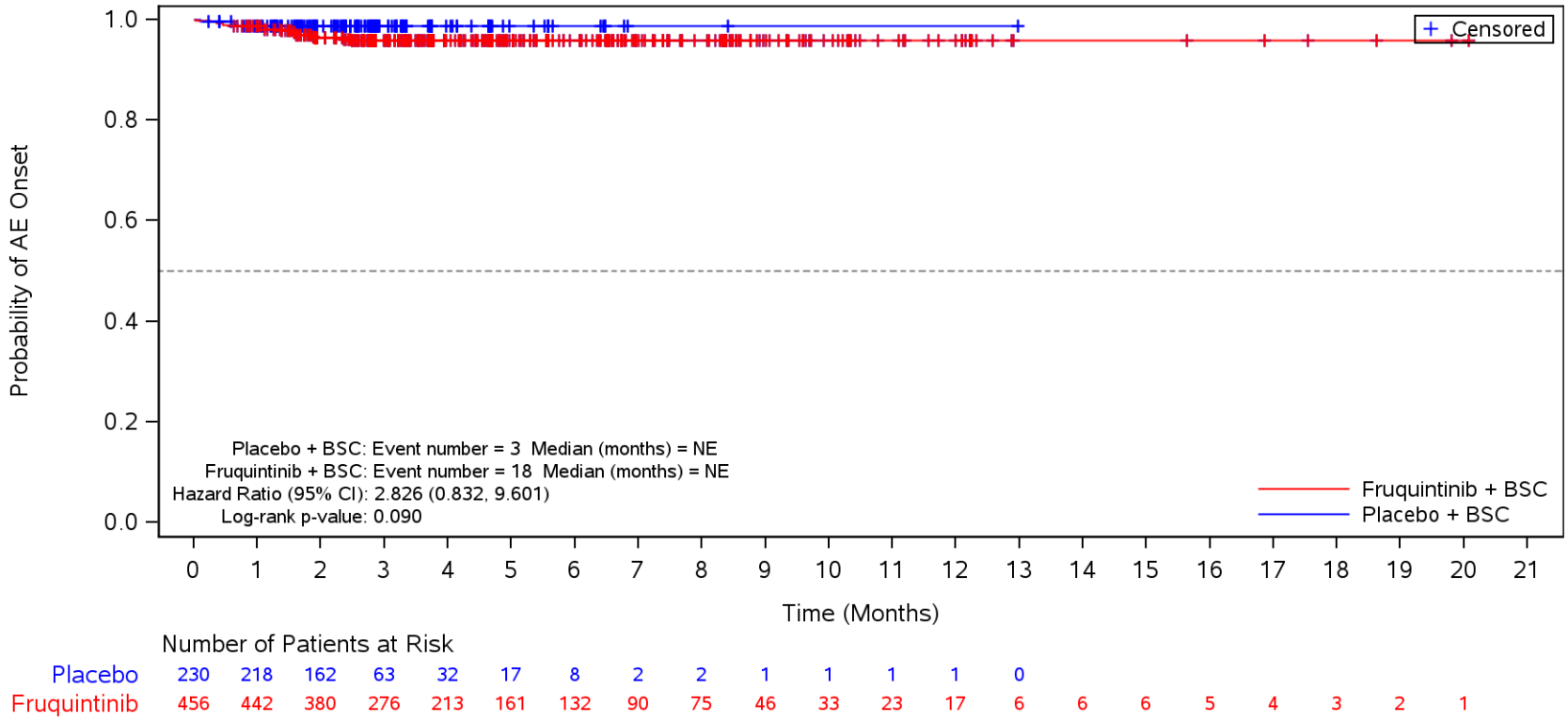
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Cough**



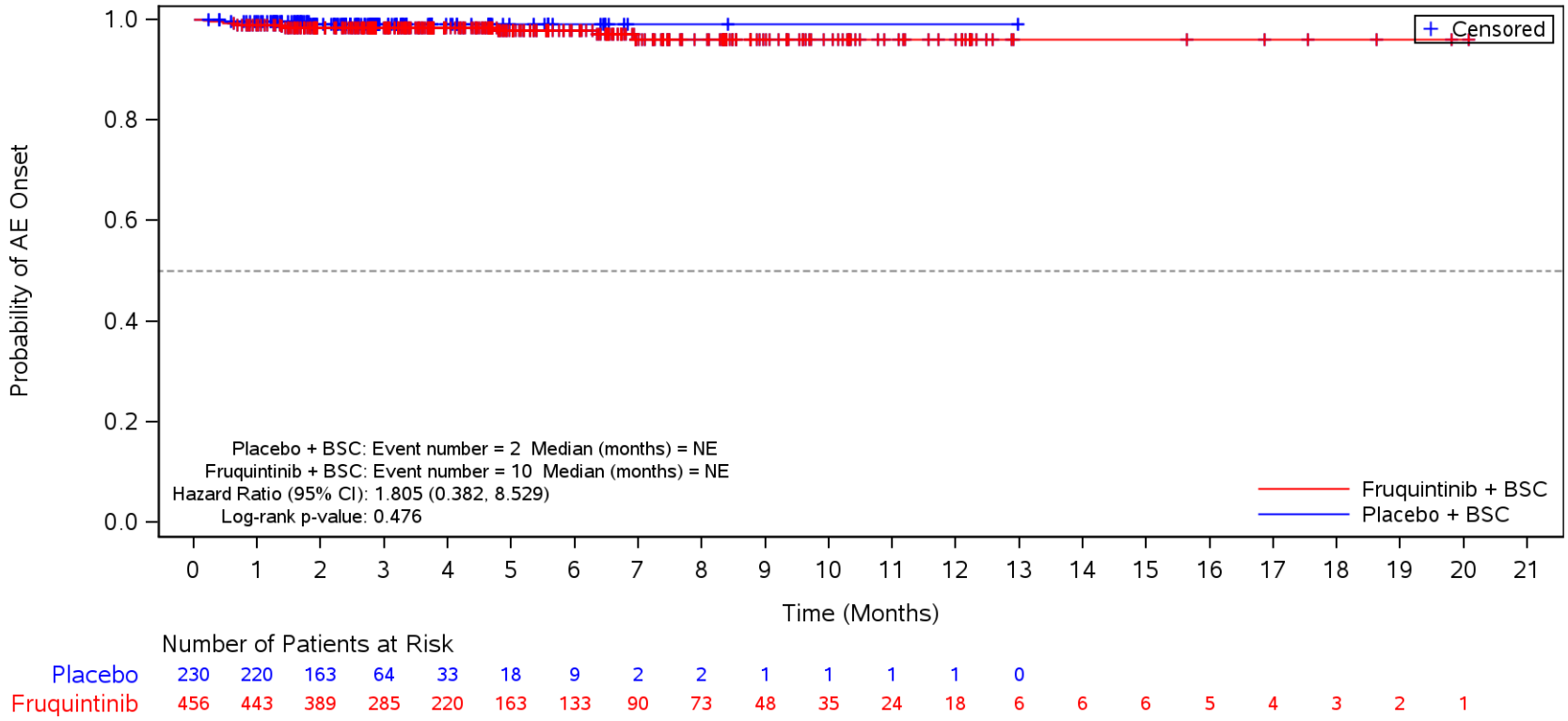
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Epistaxis**



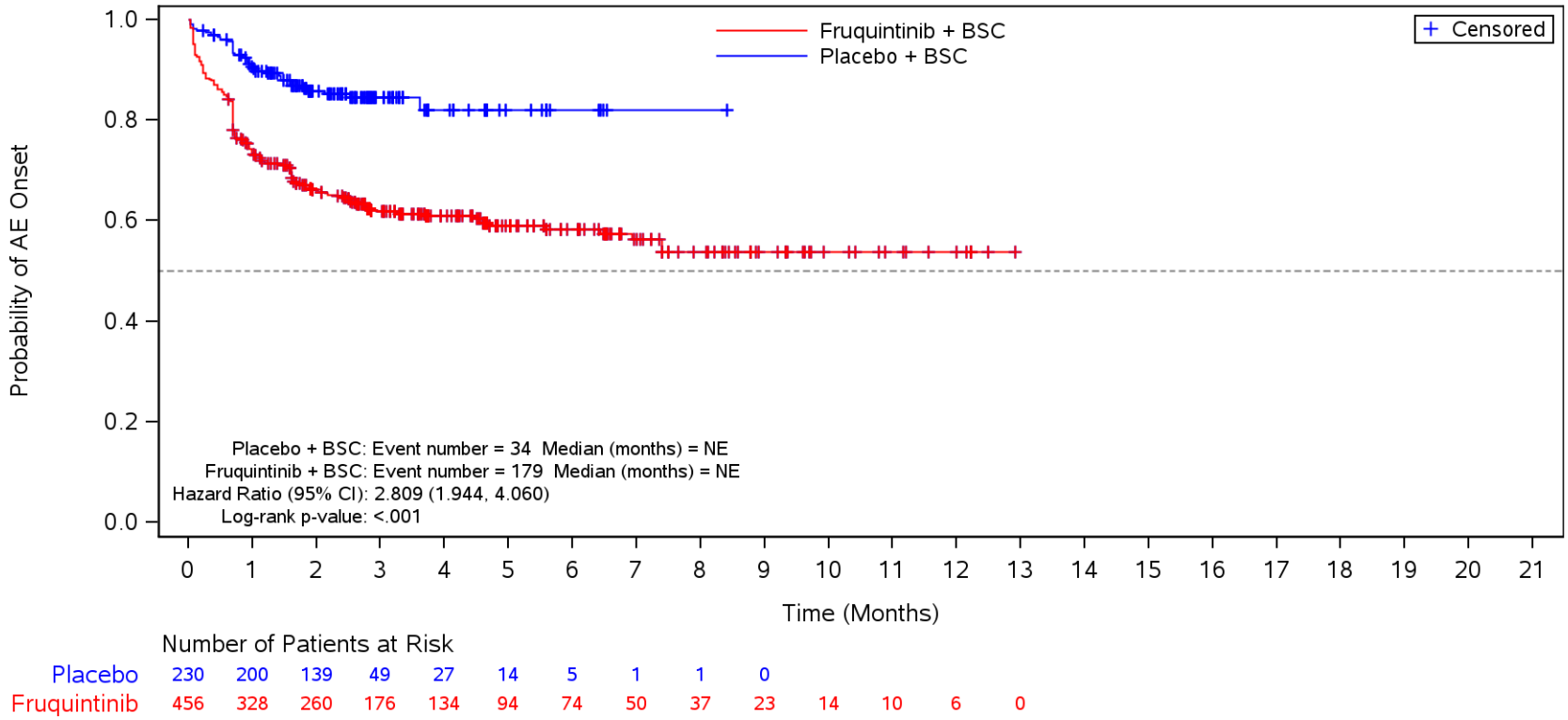
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Respiratory, thoracic and mediastinal disorders** and Preferred Term **Oropharyngeal pain**



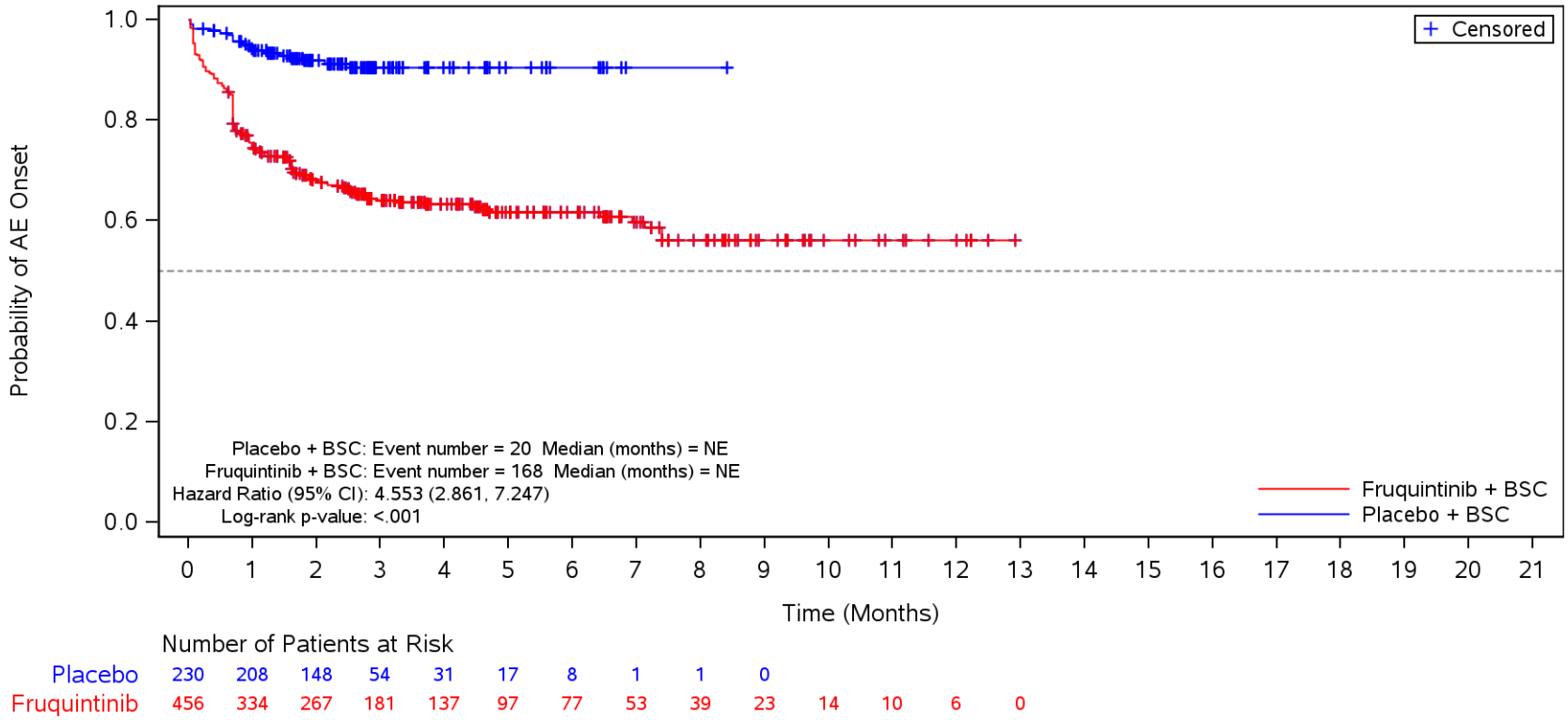
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders**



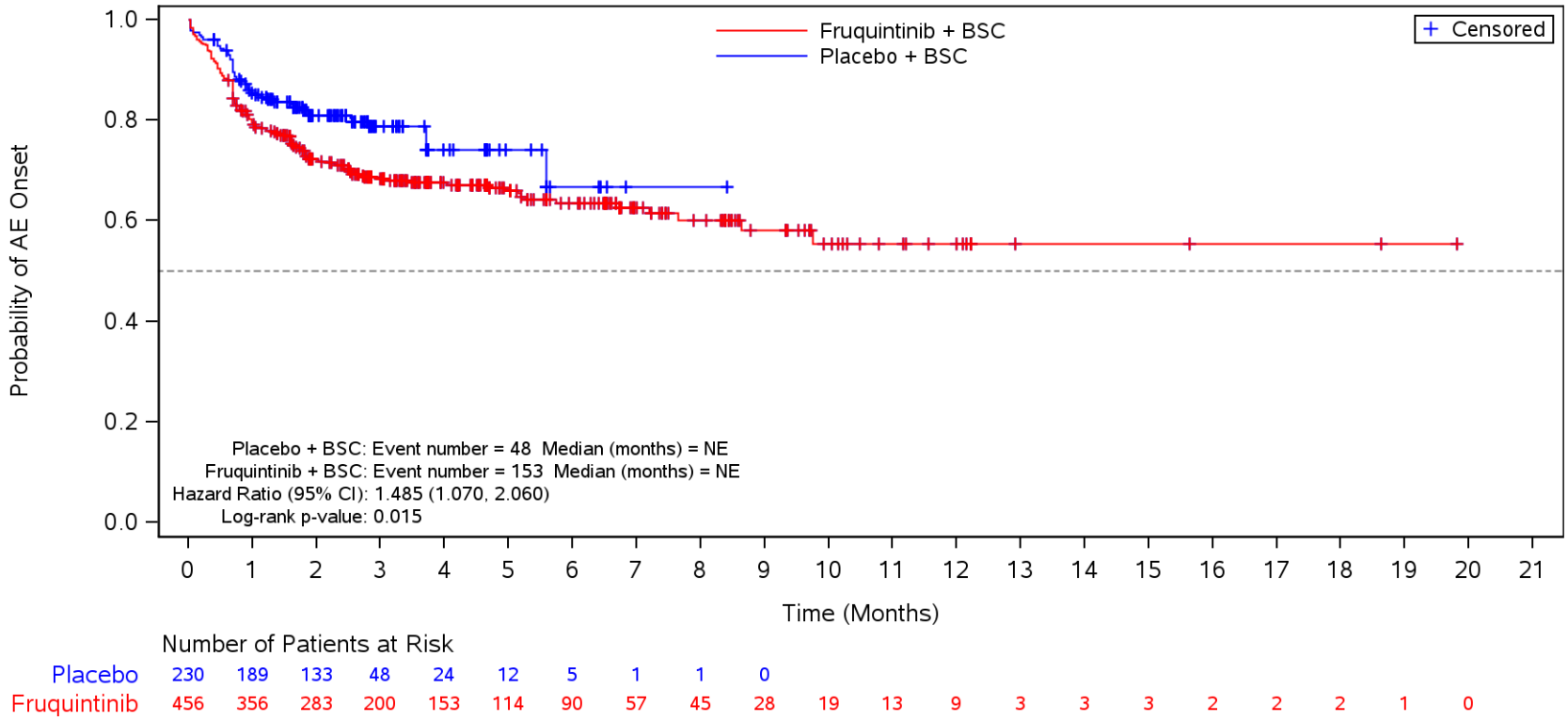
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Vascular disorders** and Preferred Term **Hypertension**



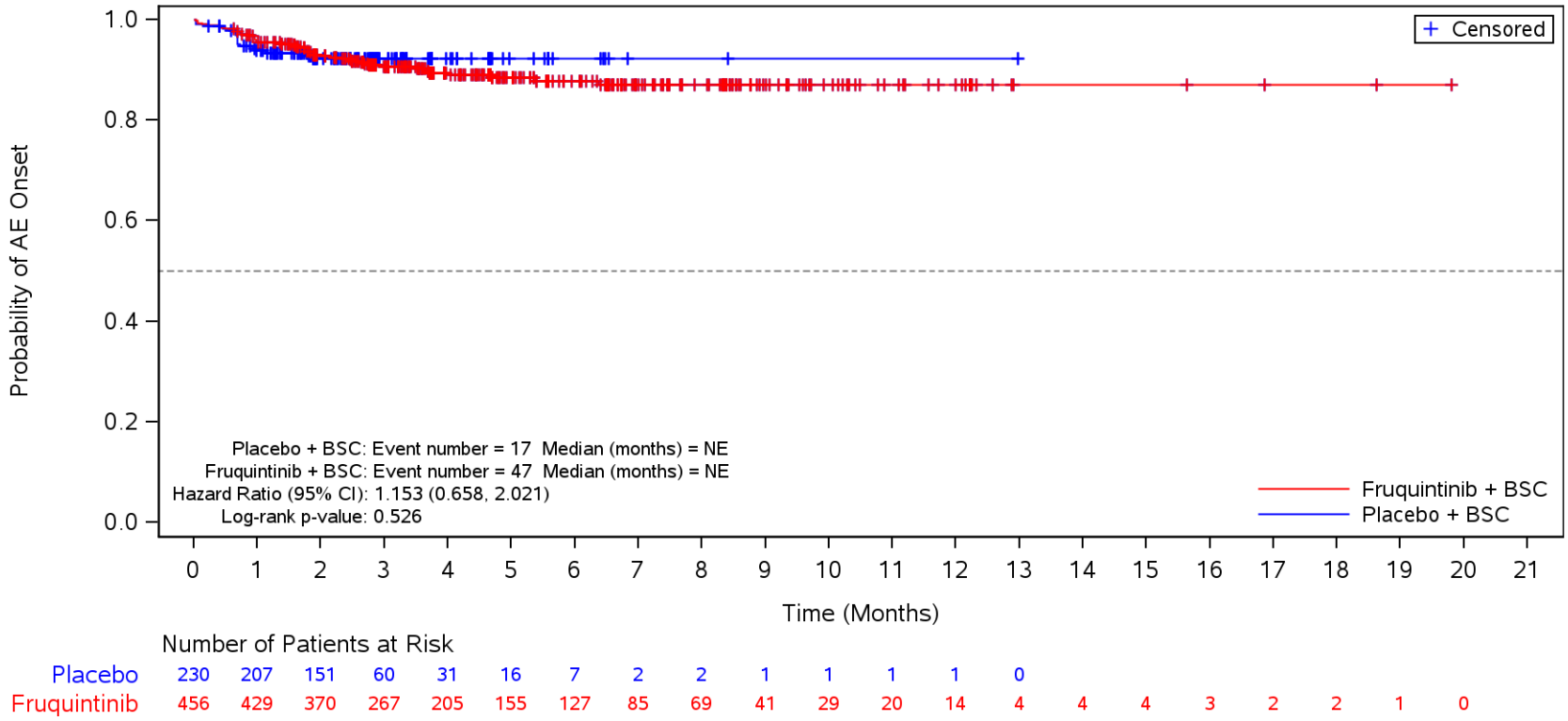
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders**



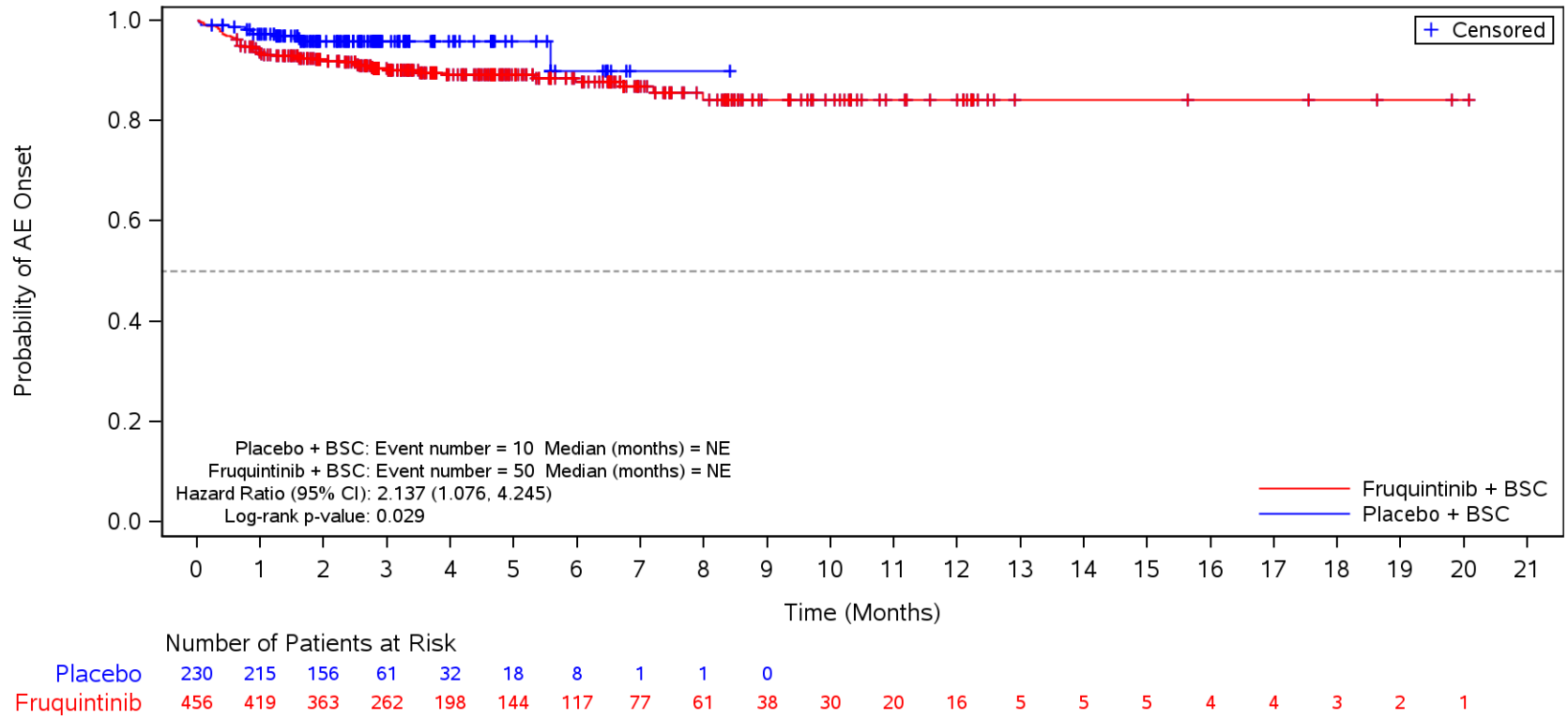
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Back pain**



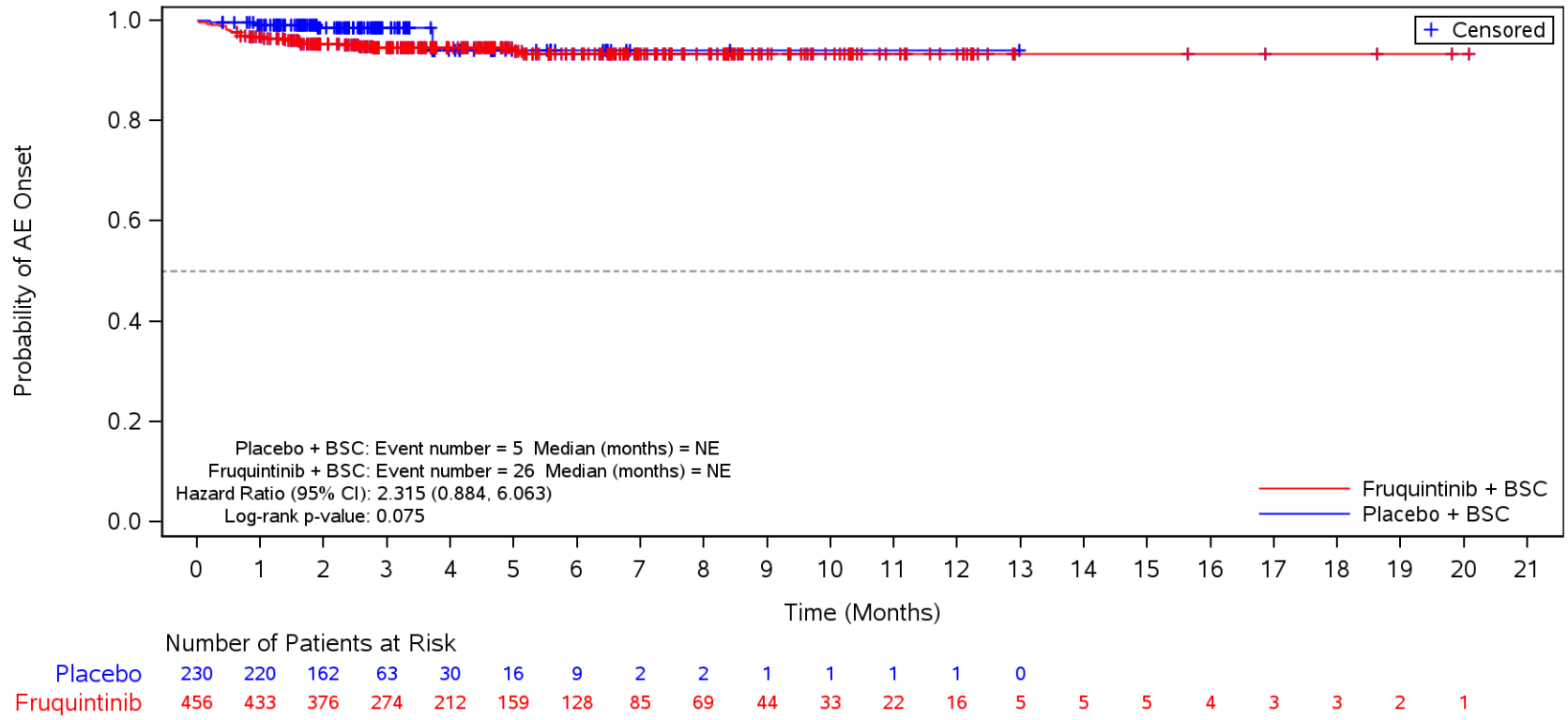
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Arthralgia**



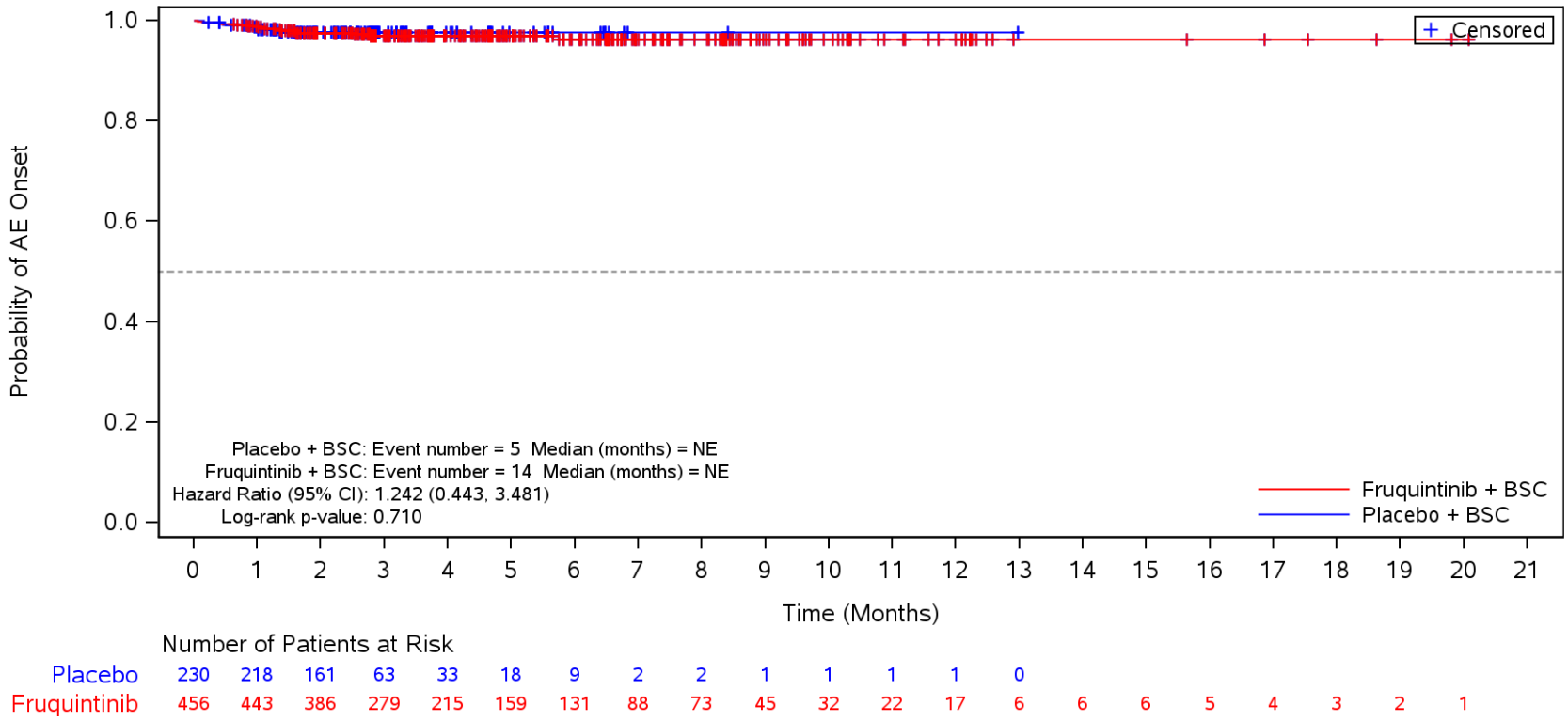
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Pain in extremity**



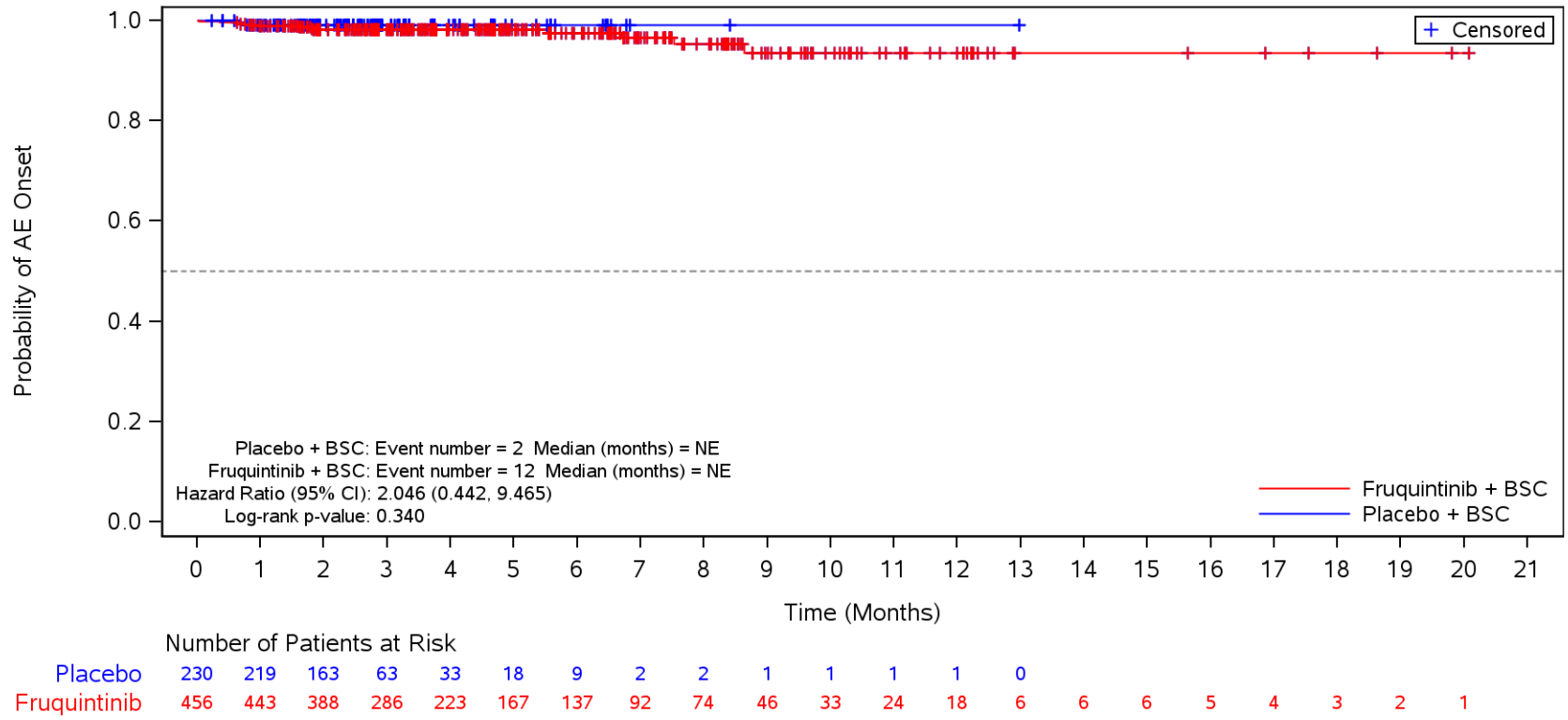
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Myalgia**



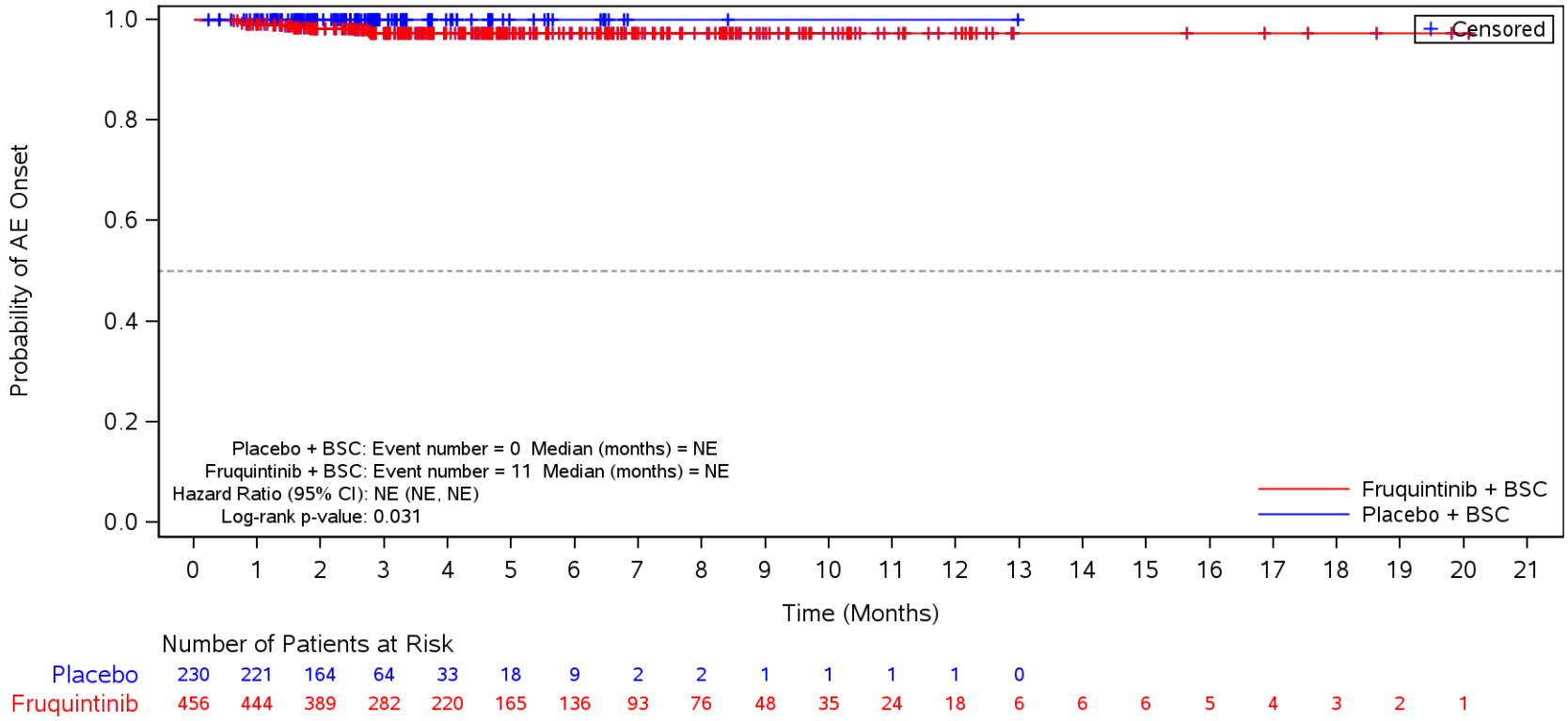
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Musculoskeletal chest pain**



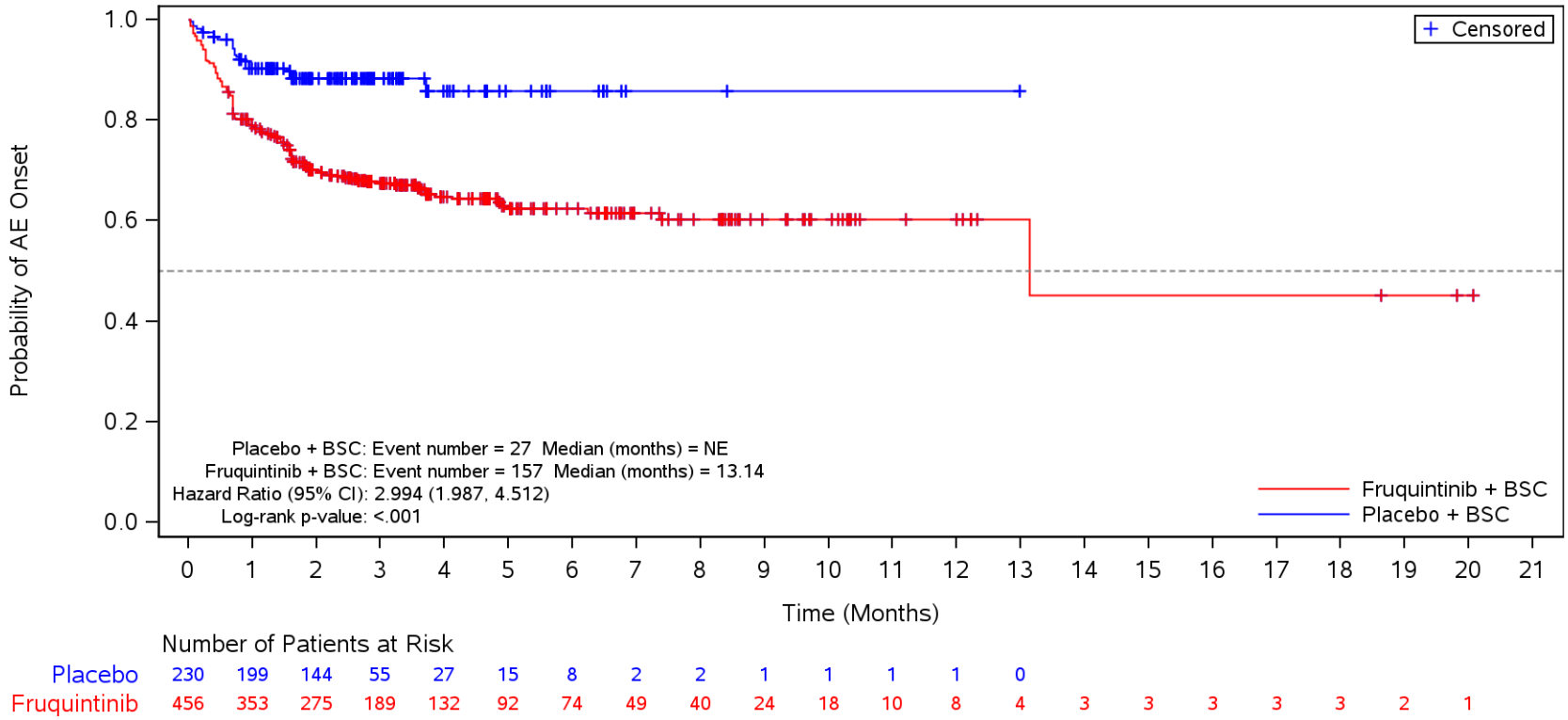
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Musculoskeletal and connective tissue disorders** and Preferred Term **Muscle spasms**



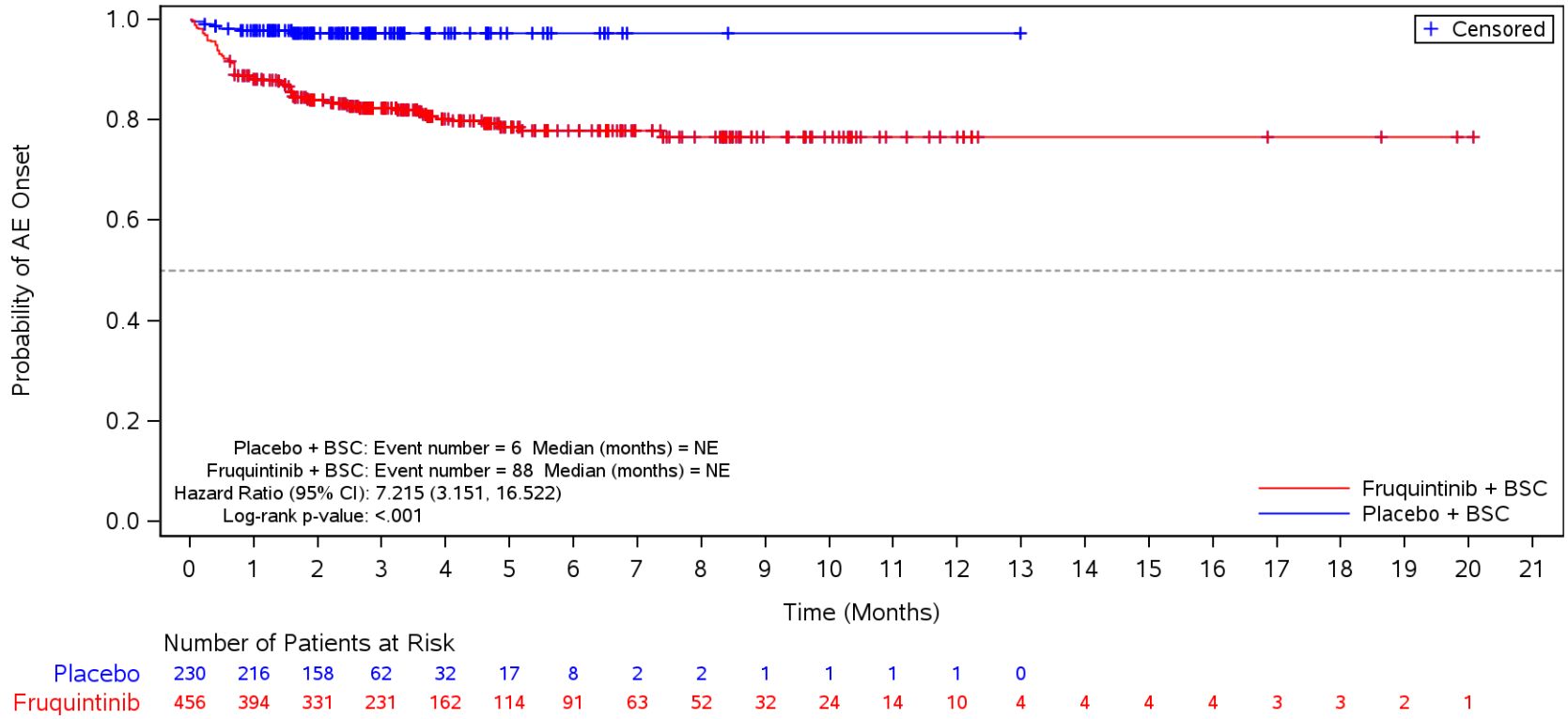
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders**



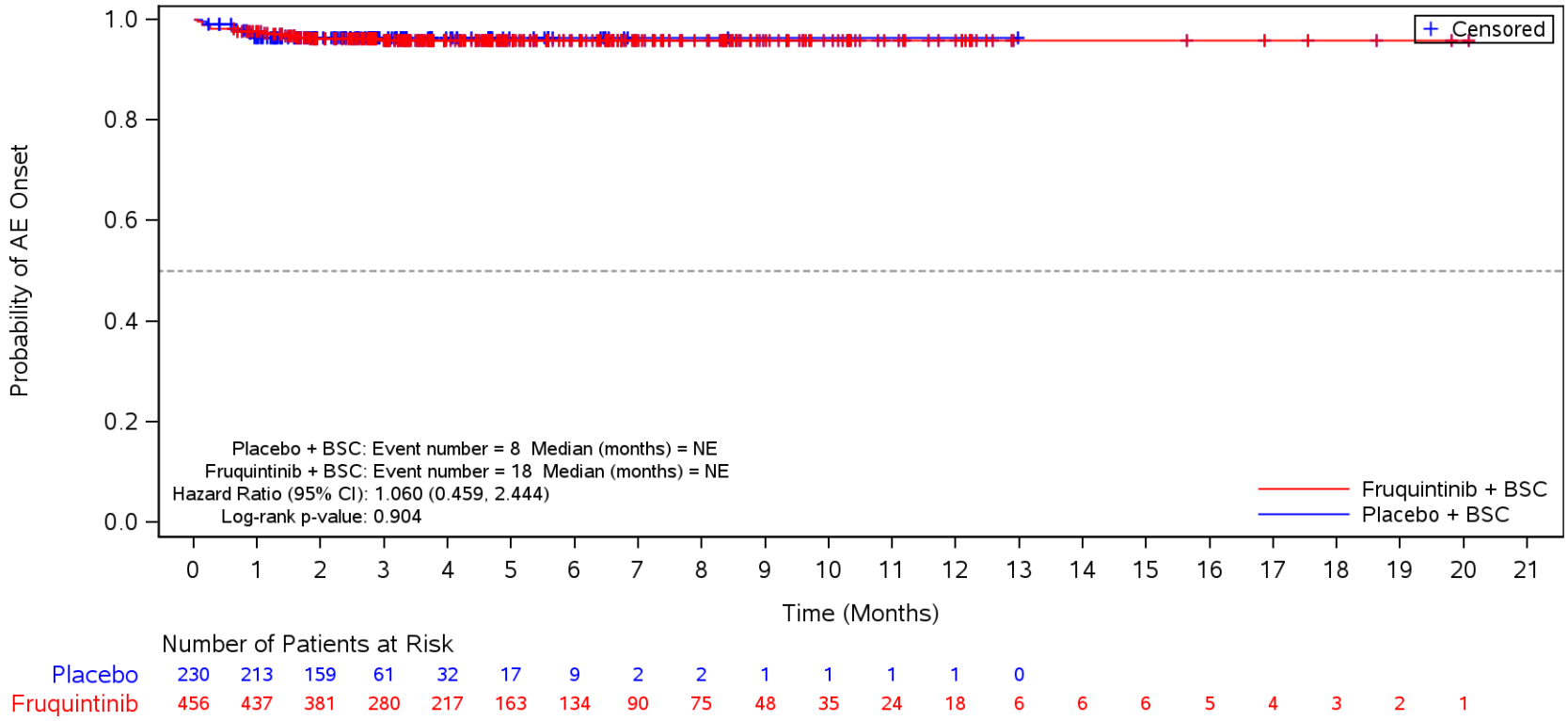
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Palmar-plantar erythrodysaesthesia syndrome**



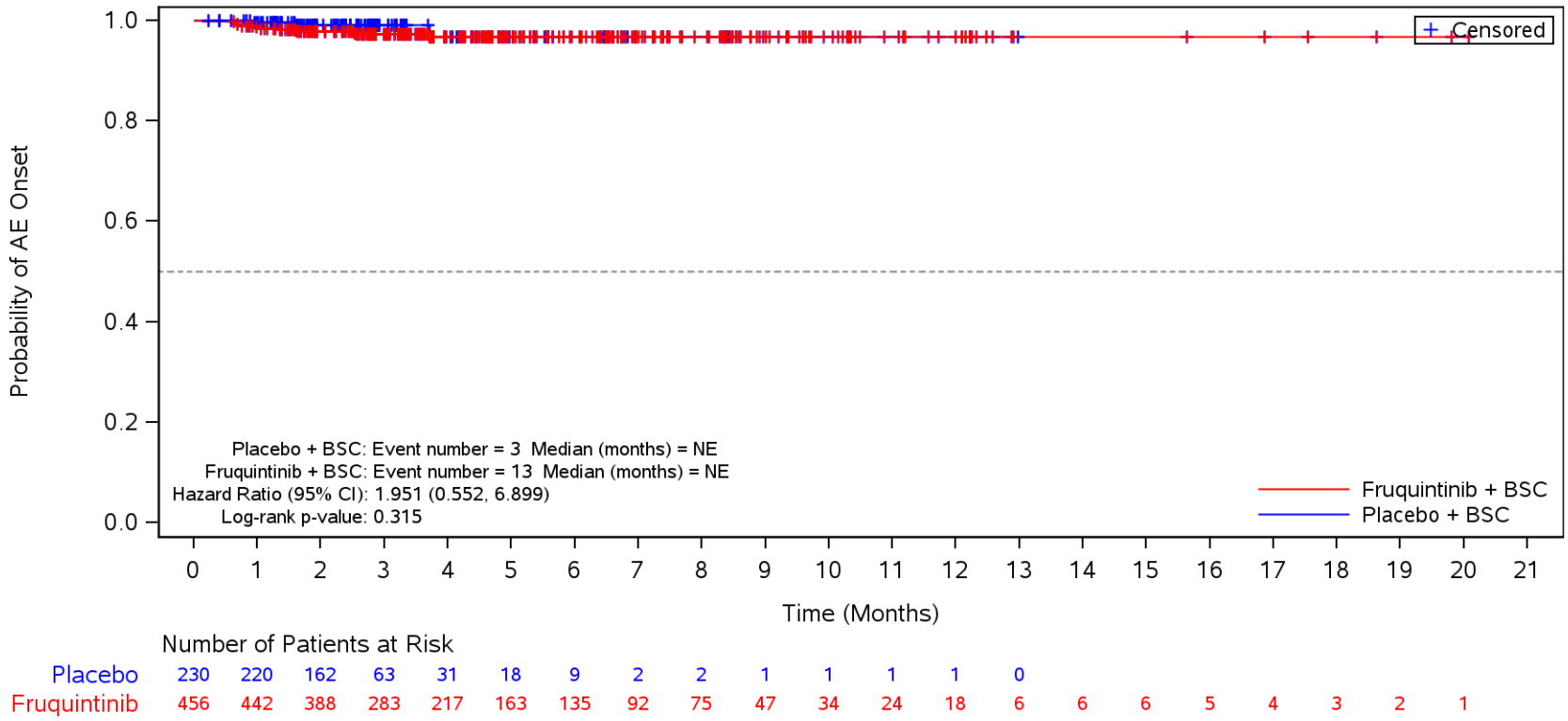
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Rash**



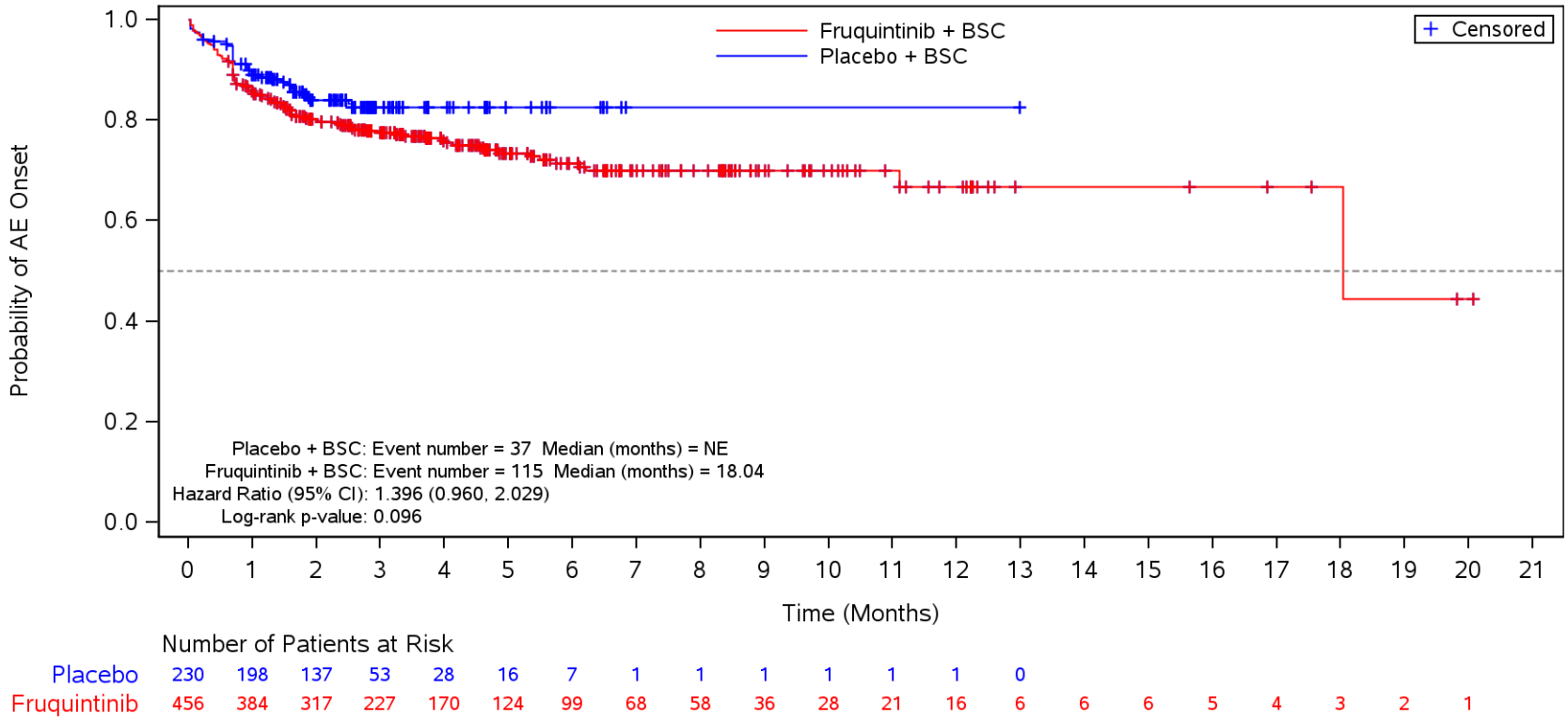
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Dry skin**



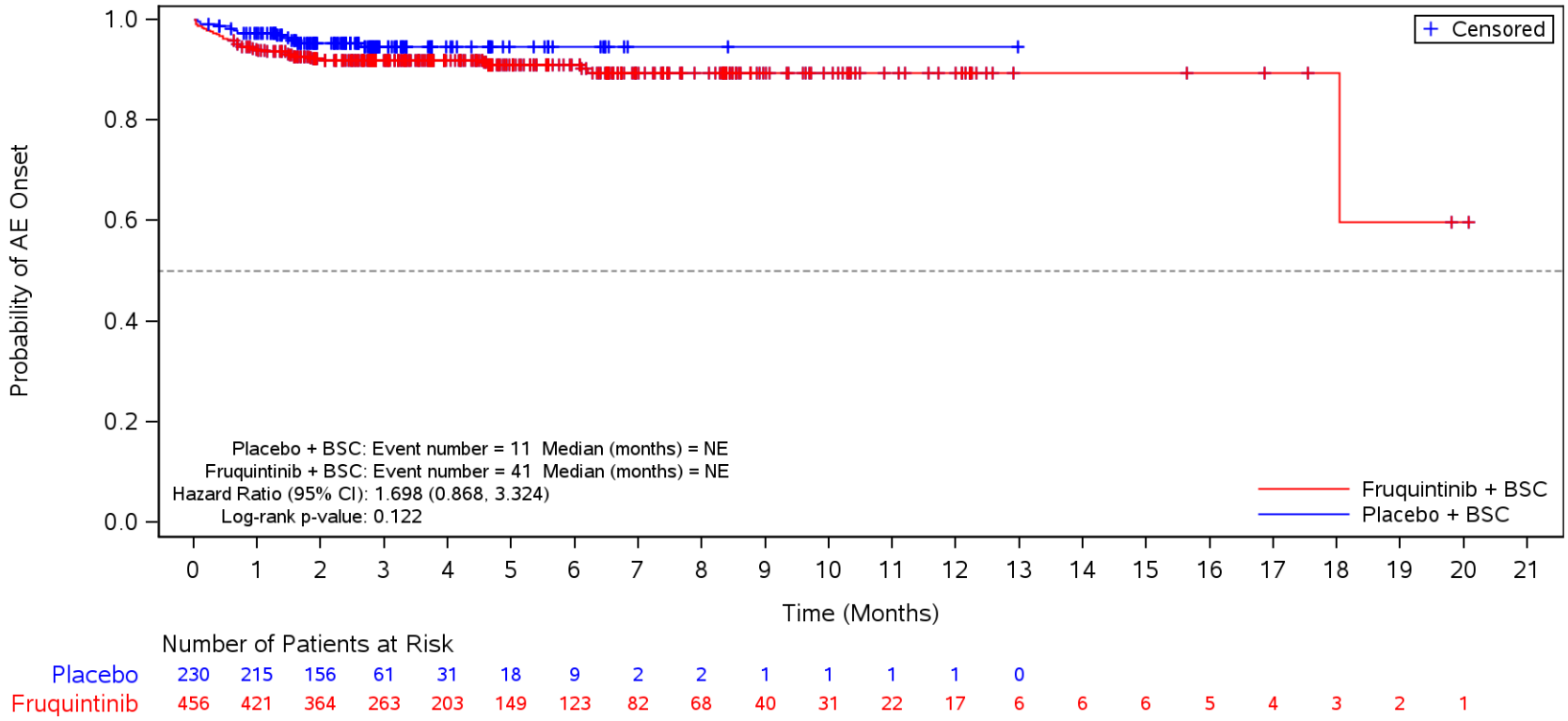
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders**



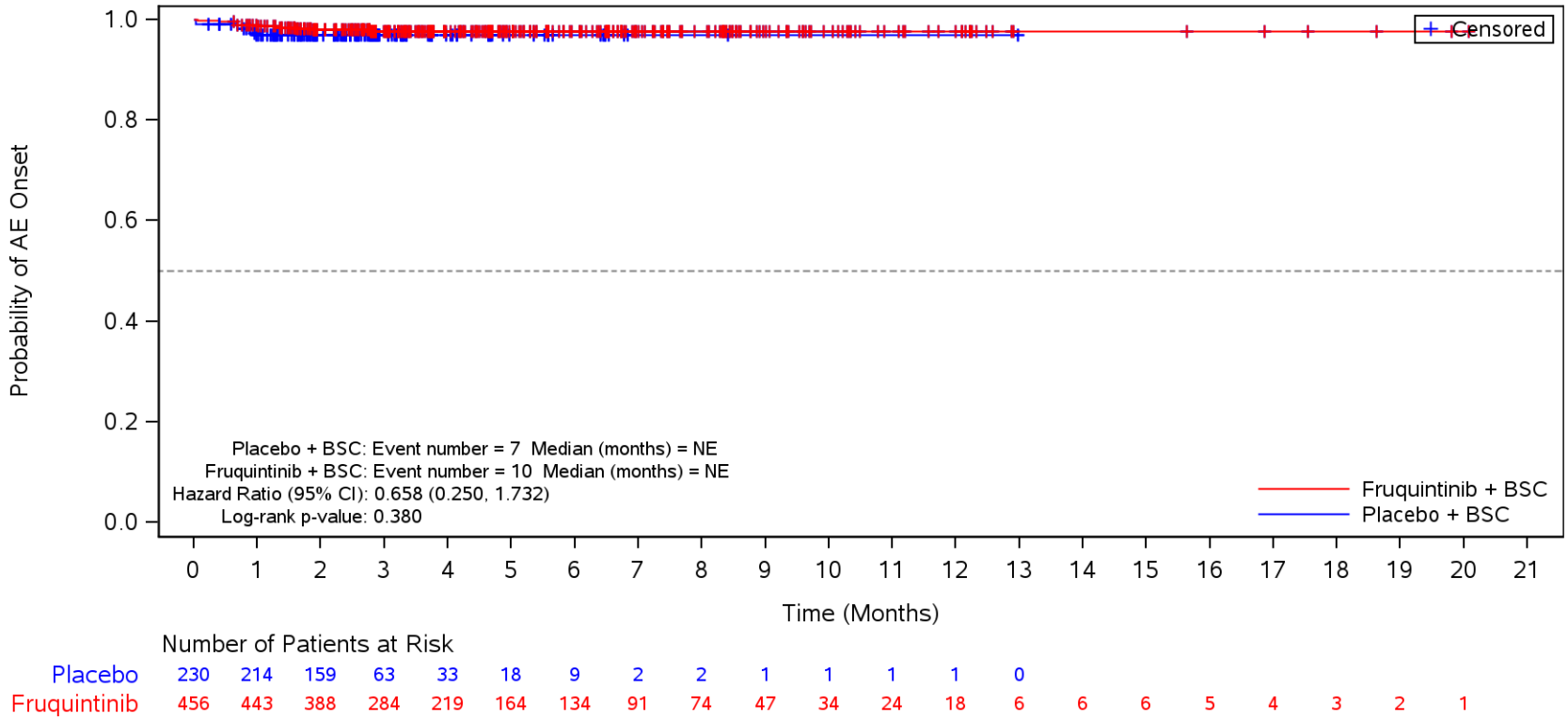
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Headache**



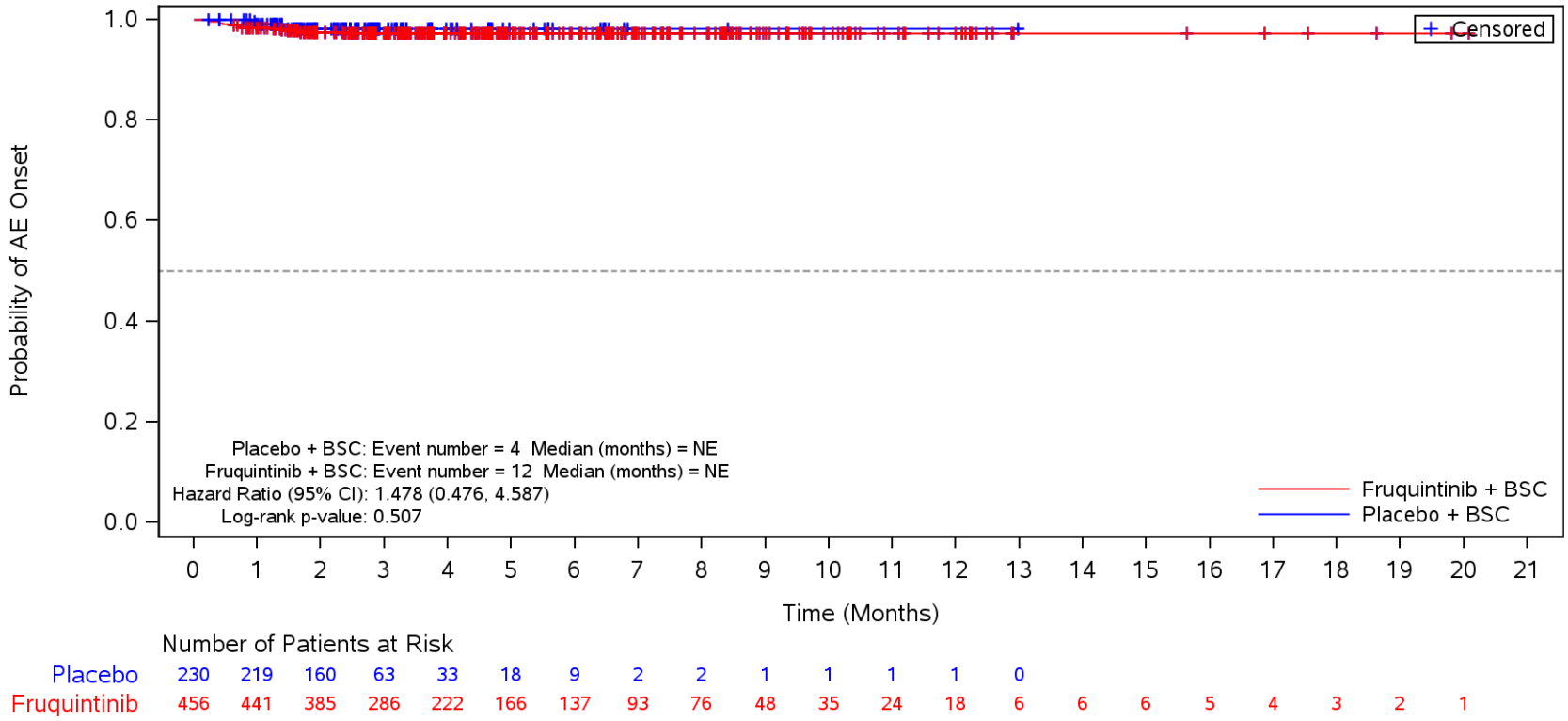
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dysgeusia**



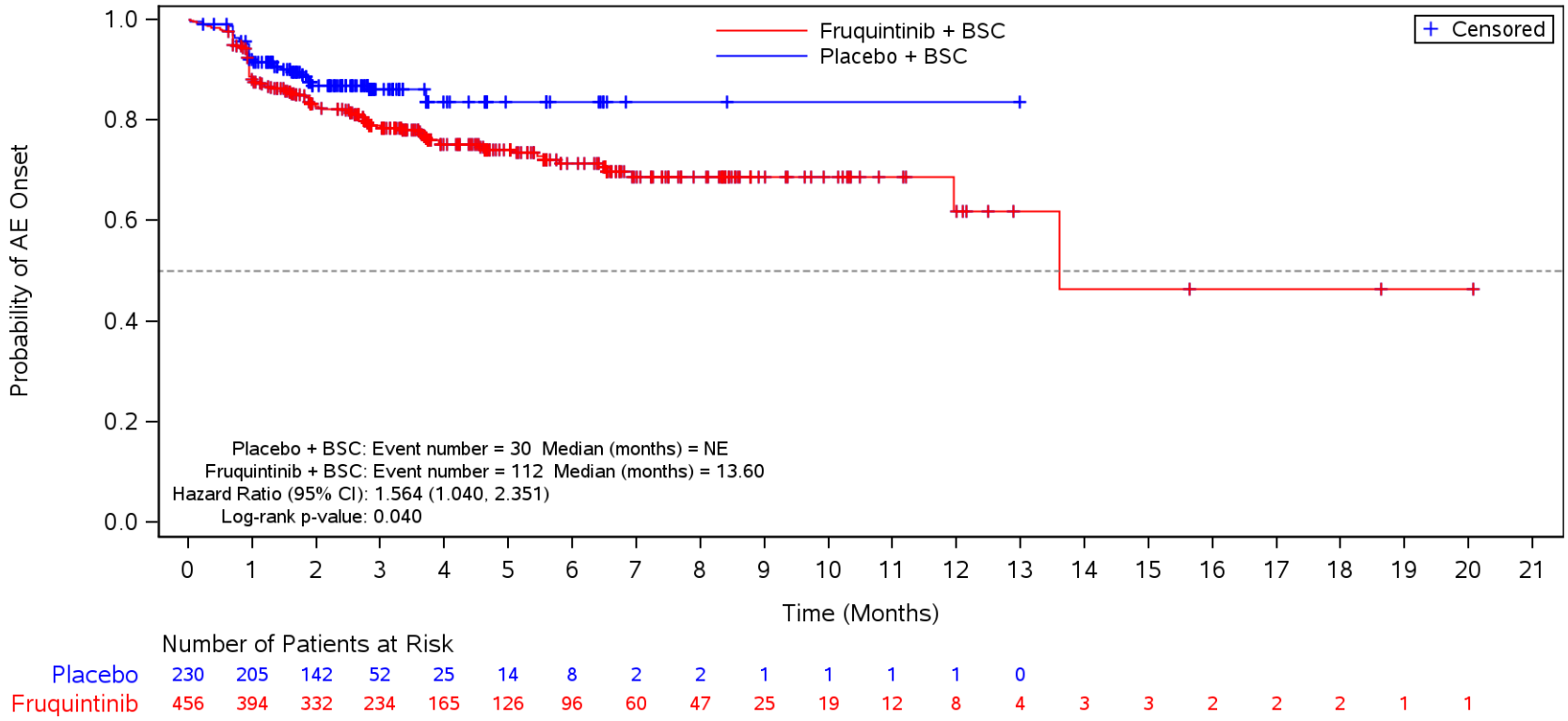
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Nervous system disorders** and Preferred Term **Dizziness**



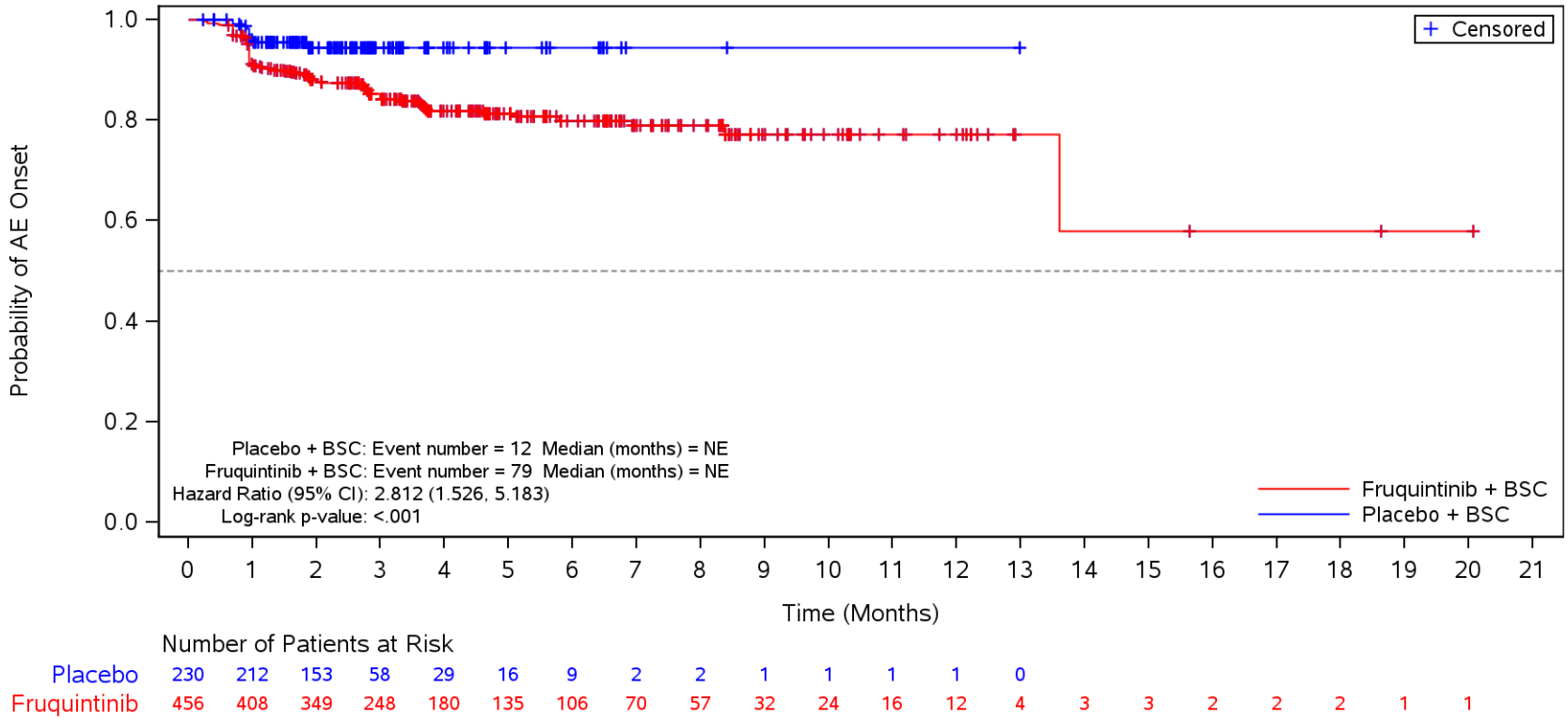
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders**



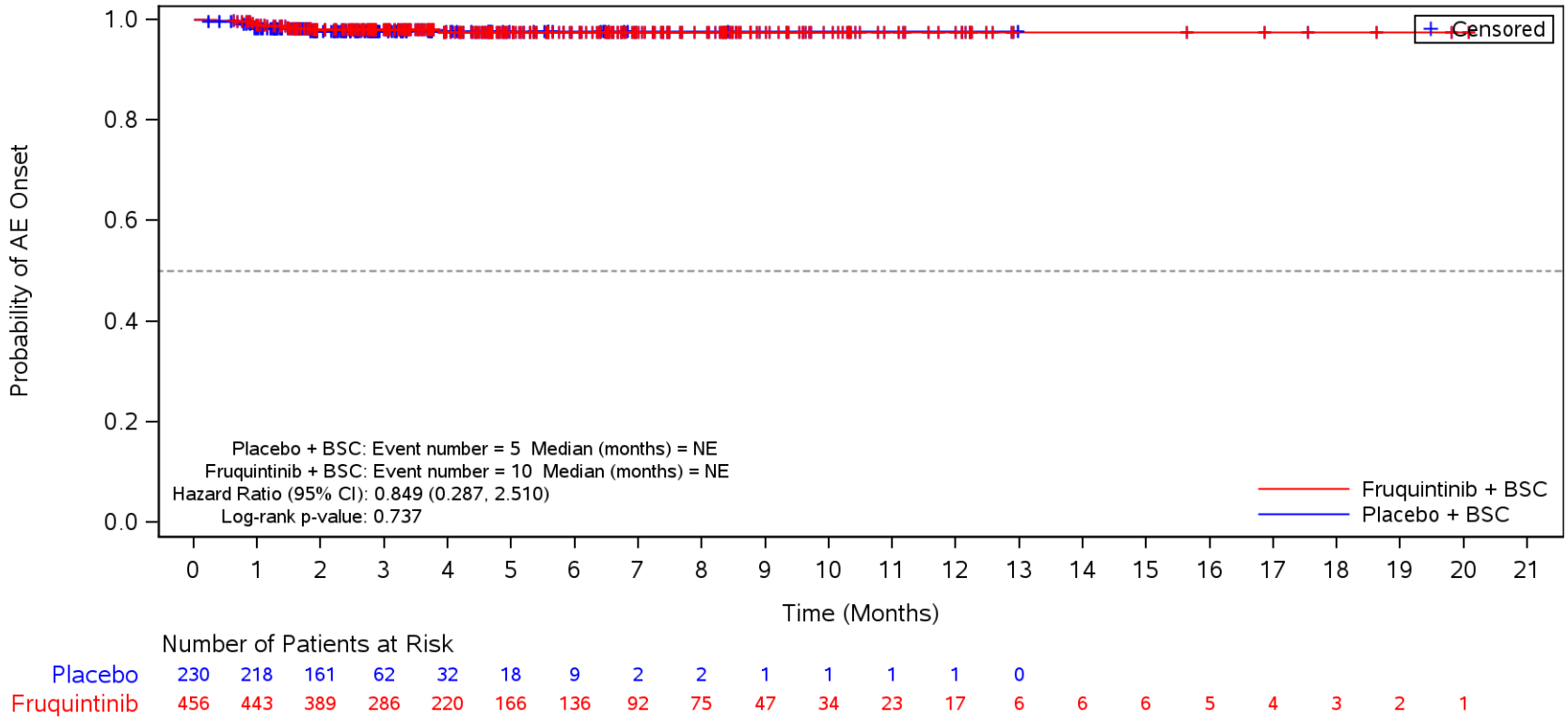
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Proteinuria**



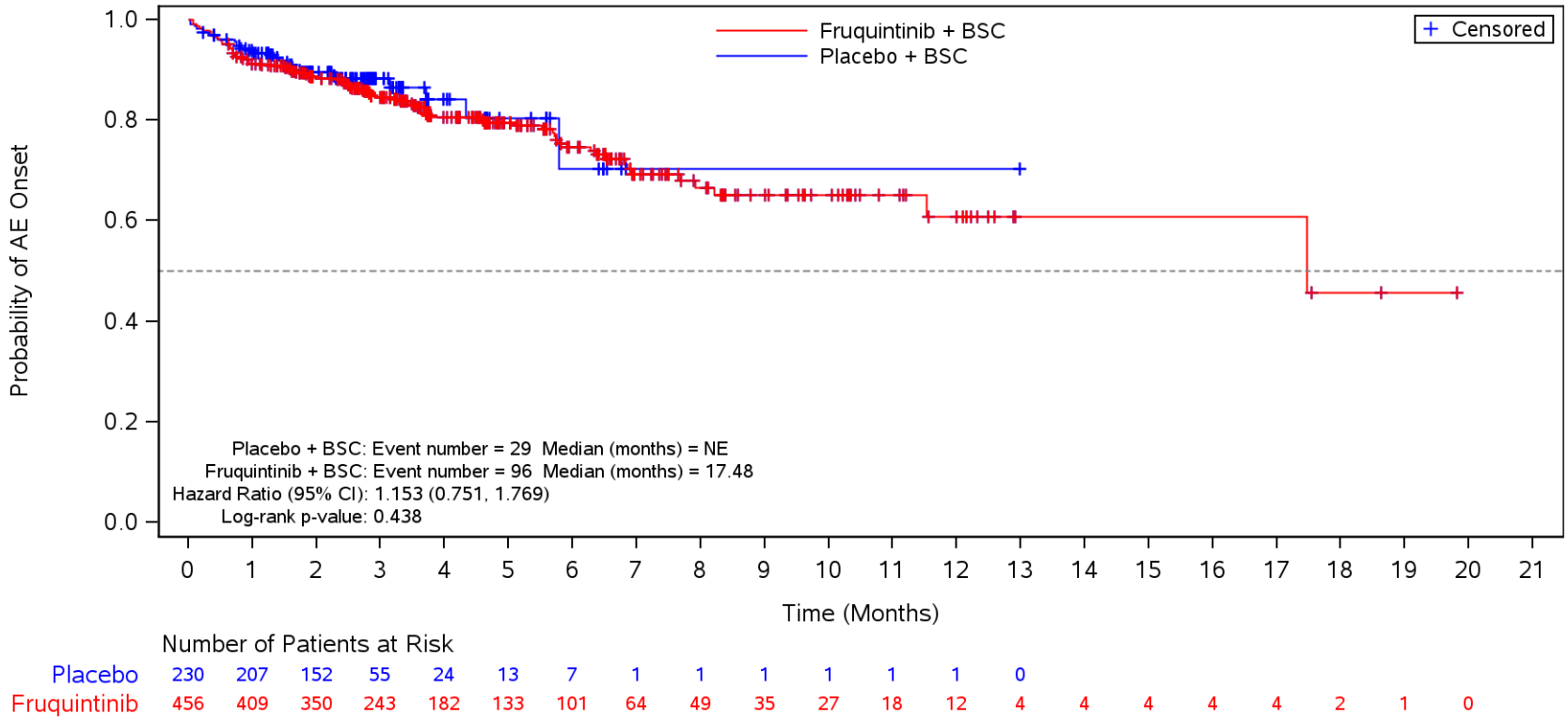
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Renal and urinary disorders** and Preferred Term **Haematuria**



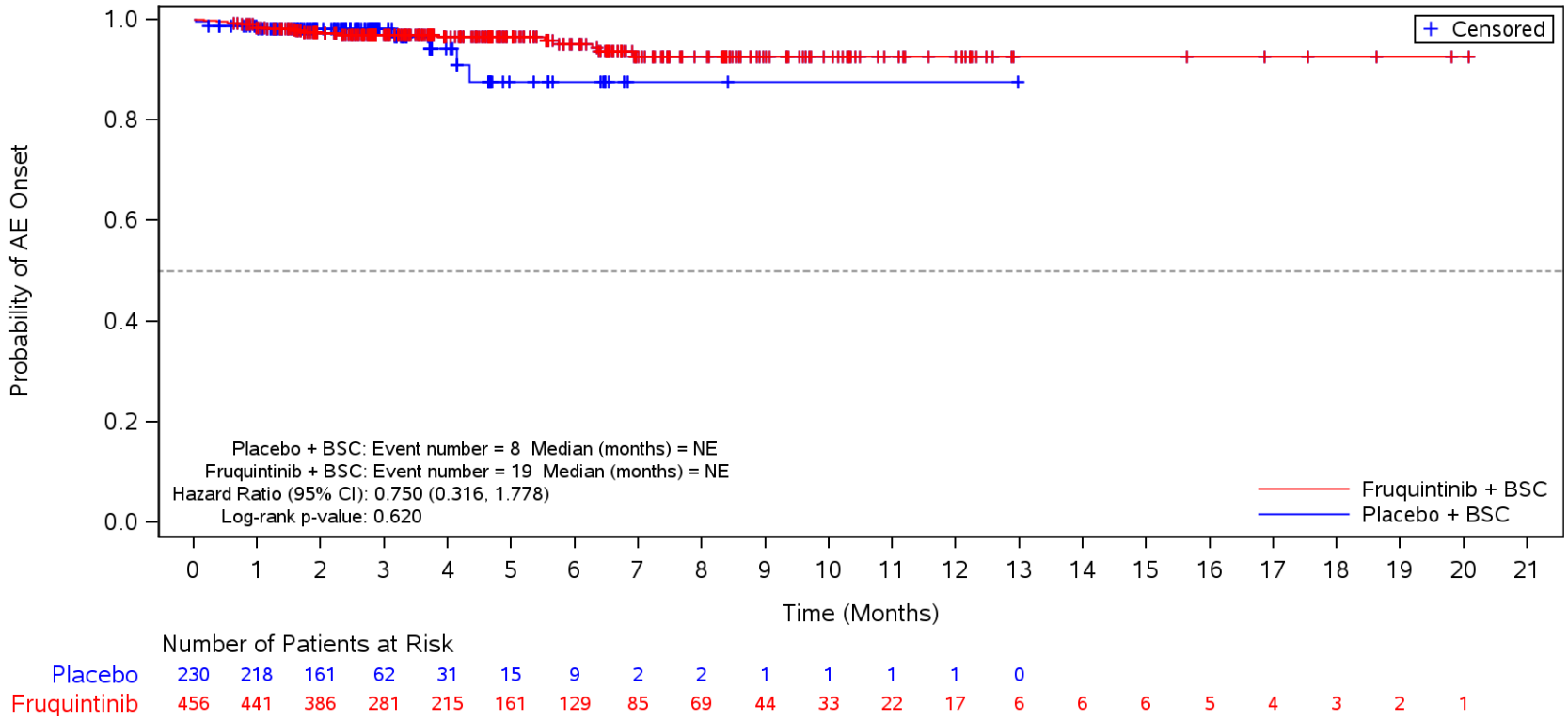
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations**



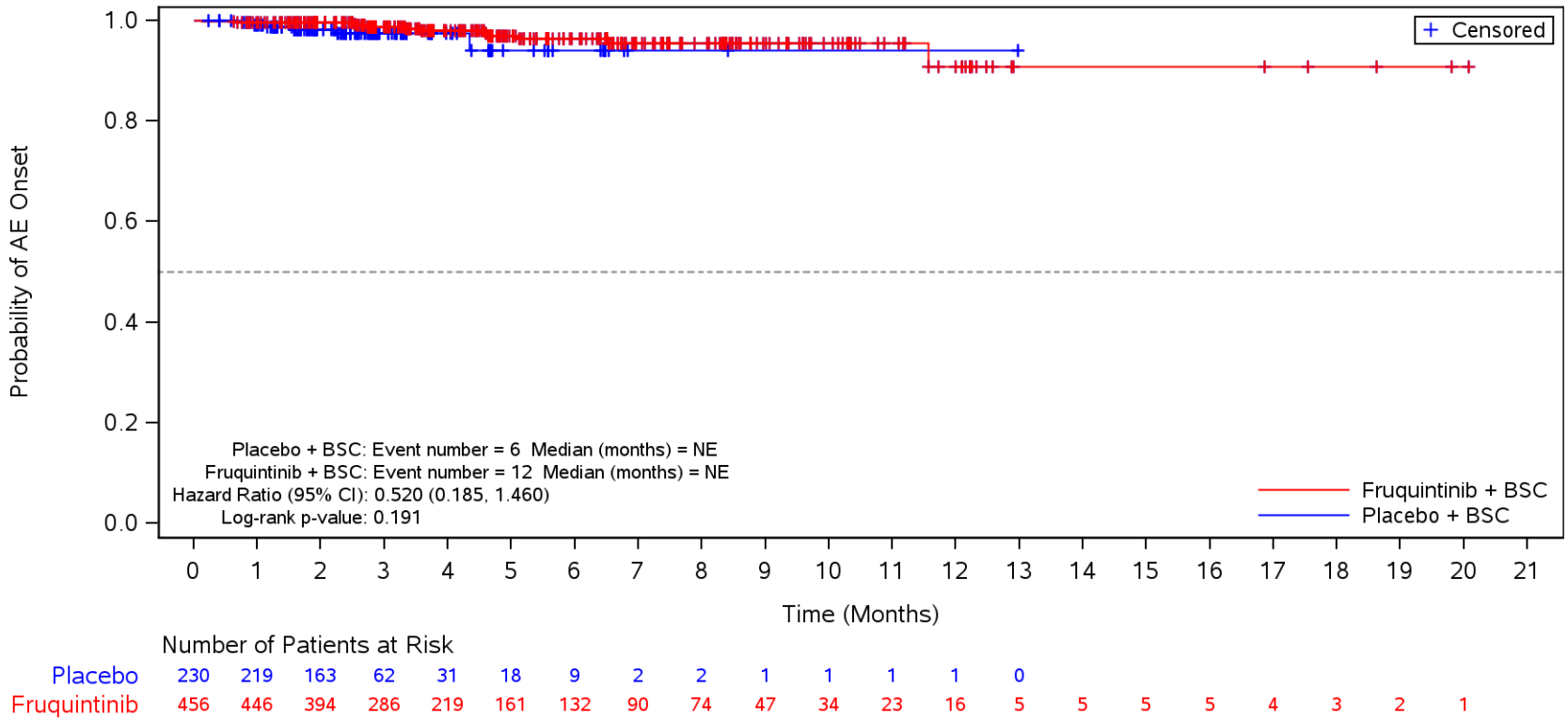
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Urinary tract infection**



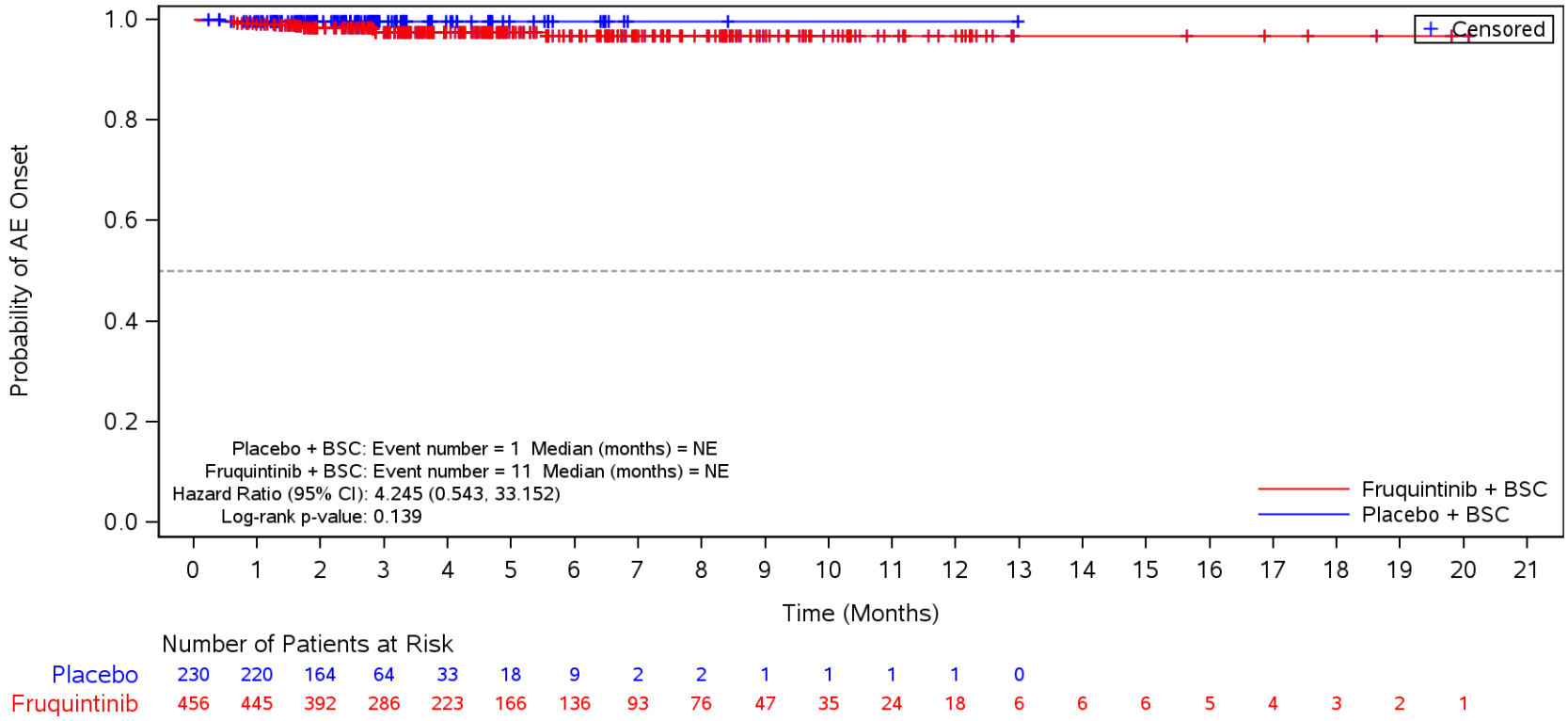
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **COVID-19**



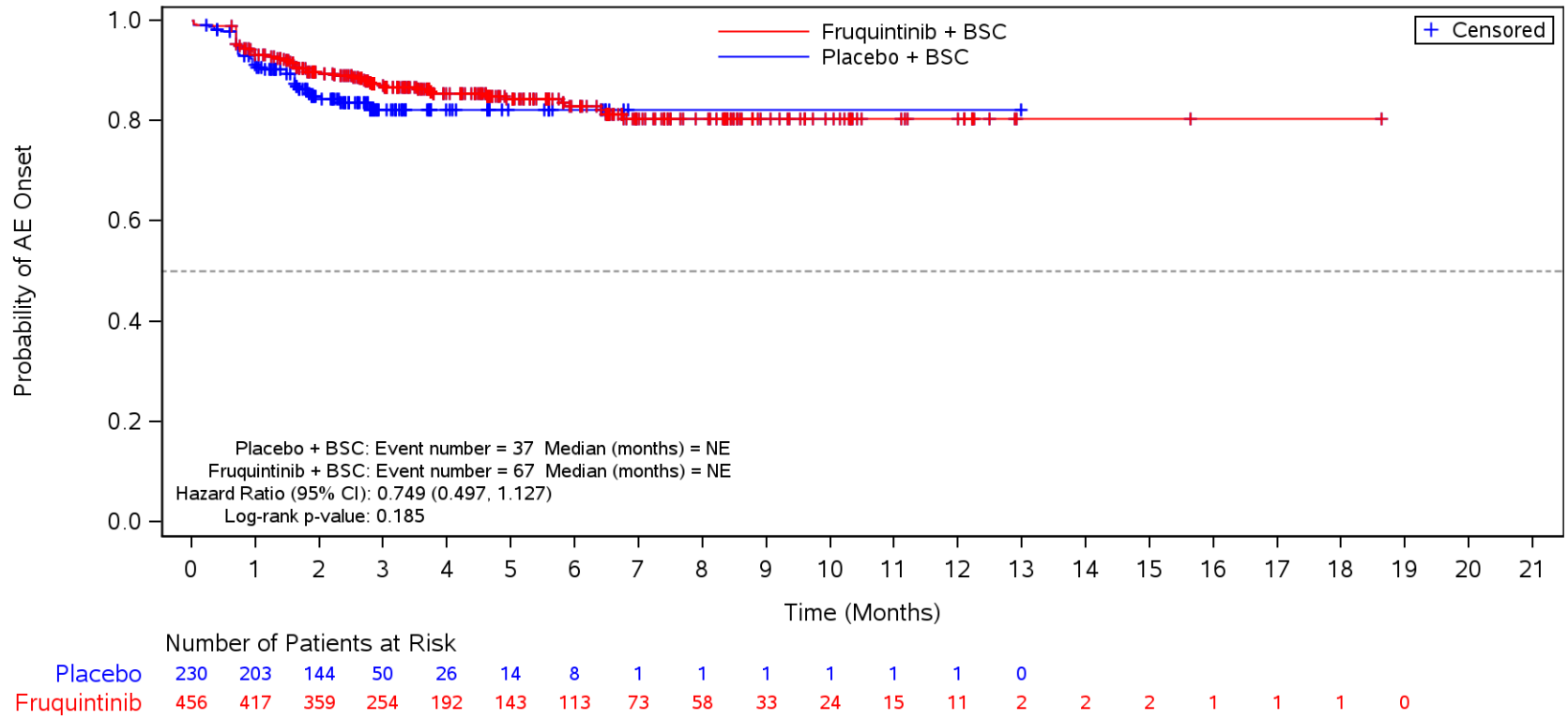
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Infections and infestations** and Preferred Term **Pneumonia**



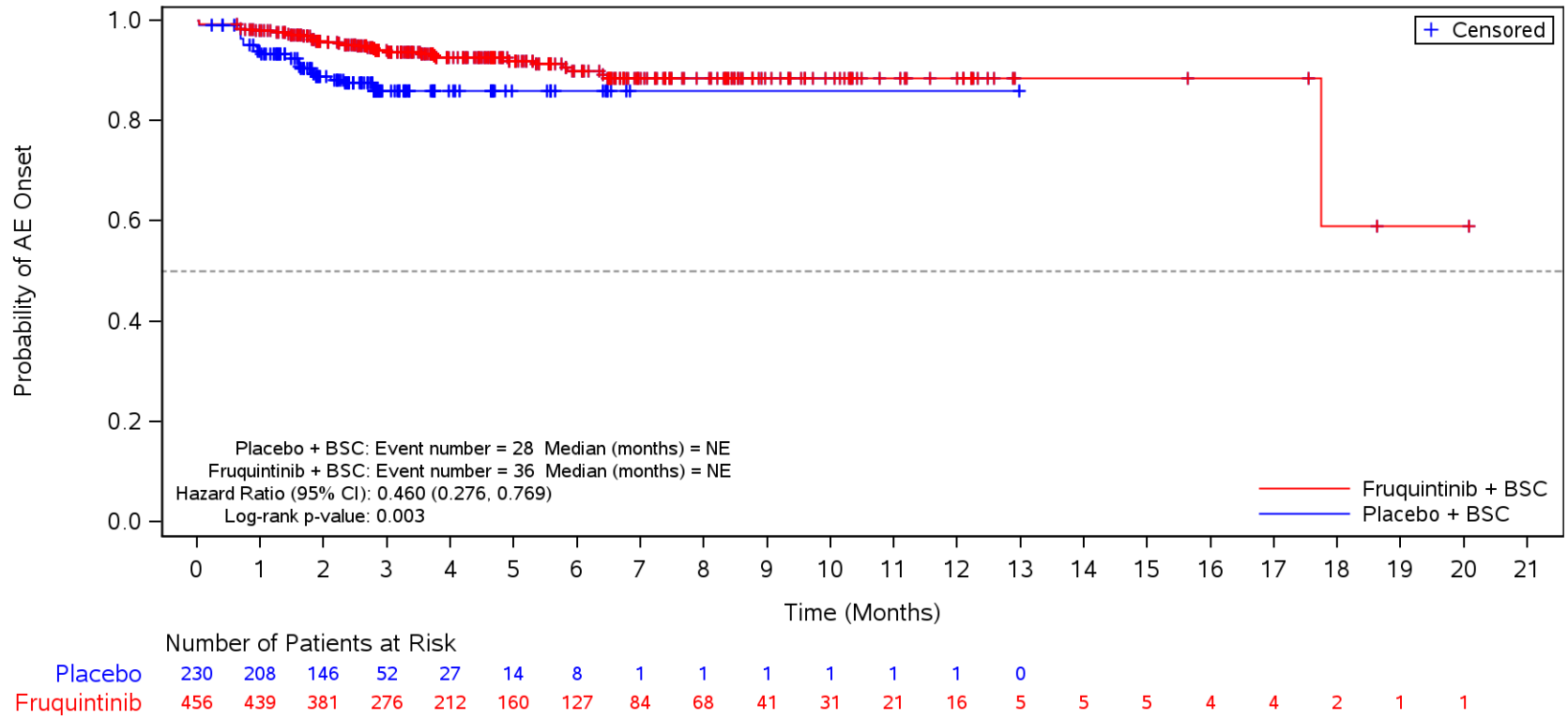
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders**



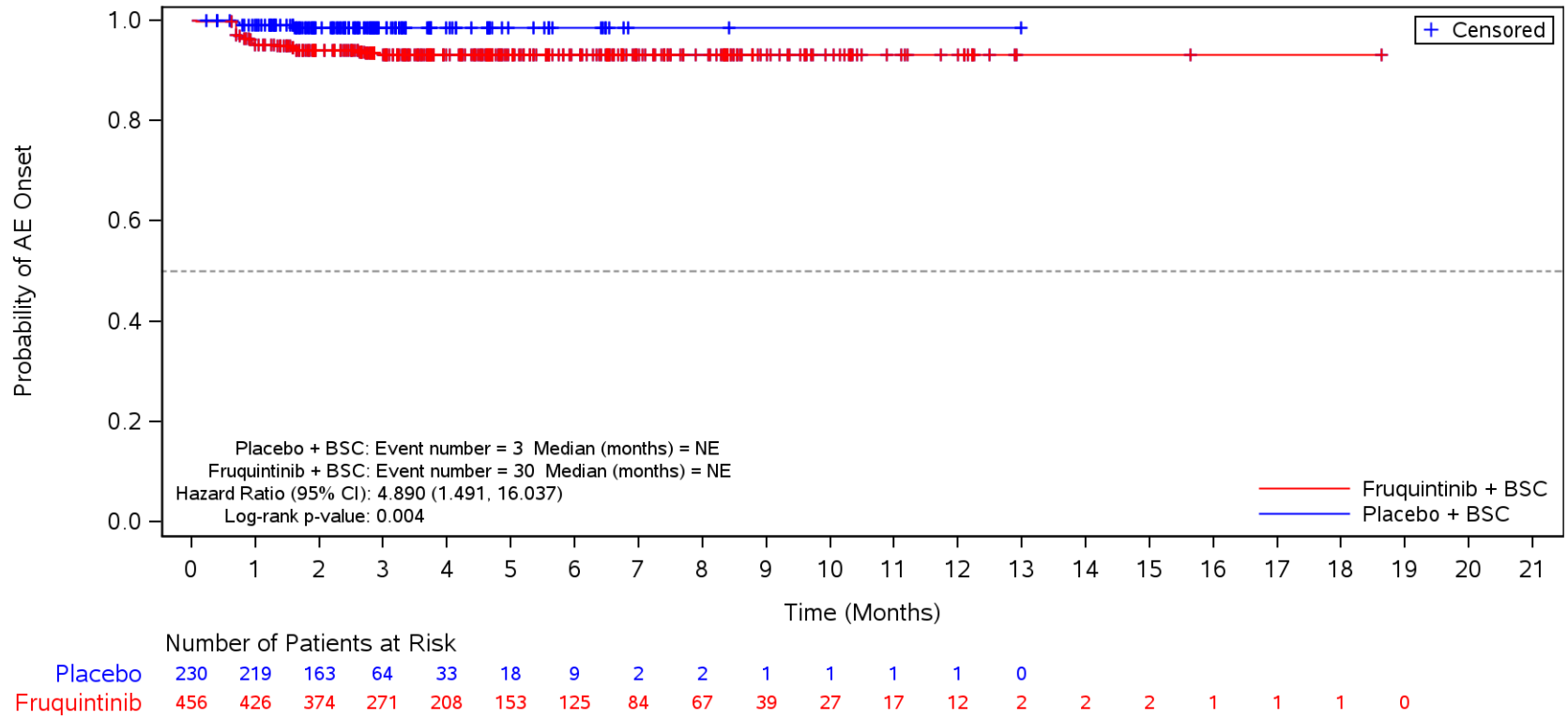
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Anaemia**



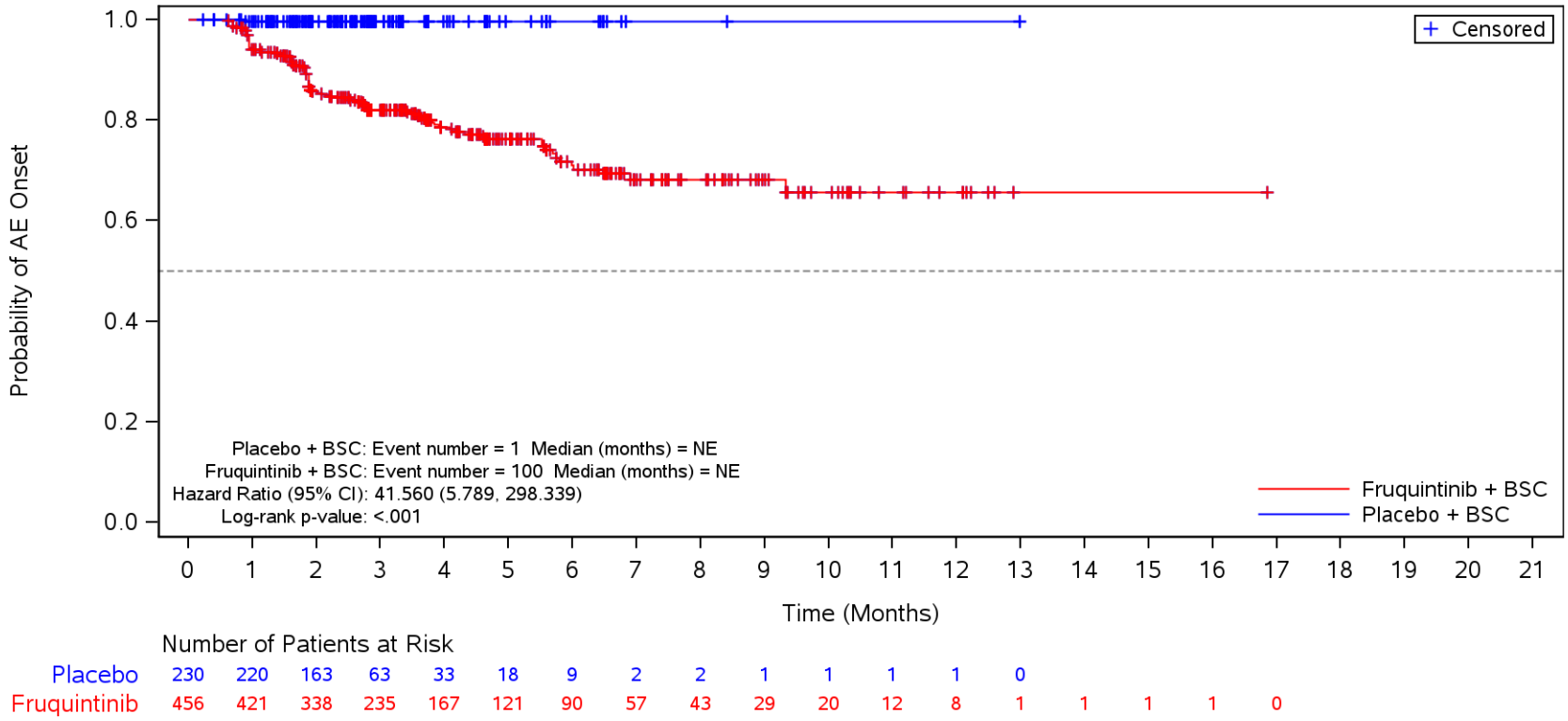
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Blood and lymphatic system disorders** and Preferred Term **Thrombocytopenia**



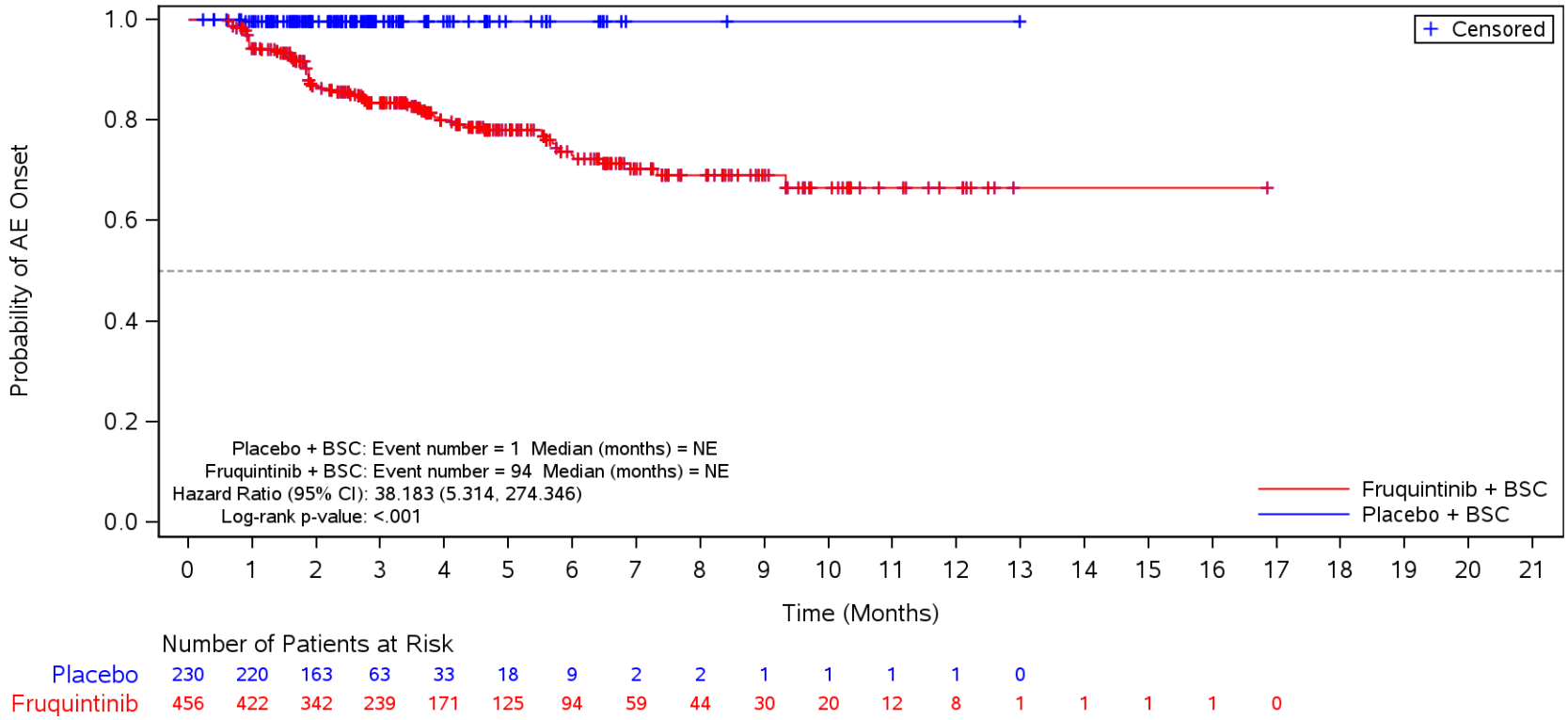
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders**



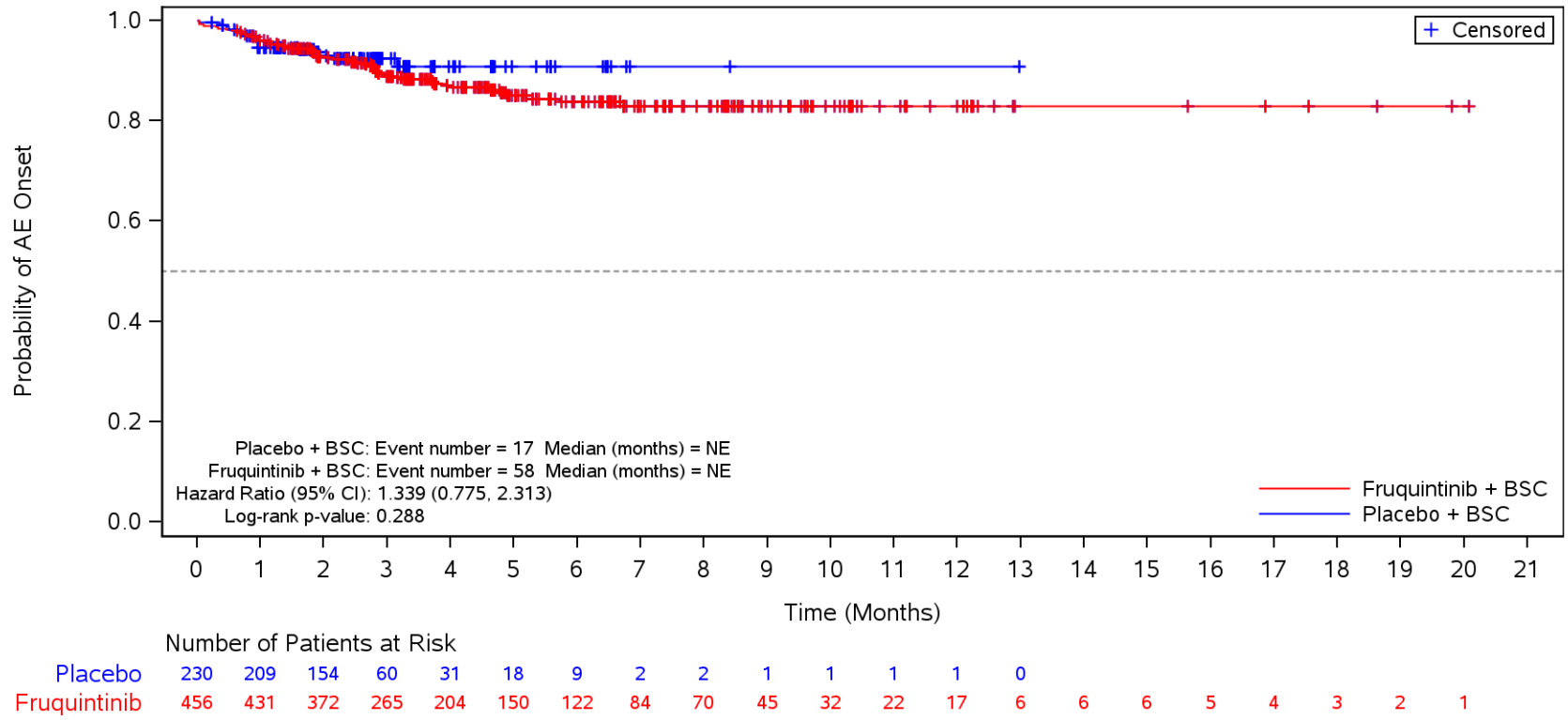
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Endocrine disorders** and Preferred Term **Hypothyroidism**



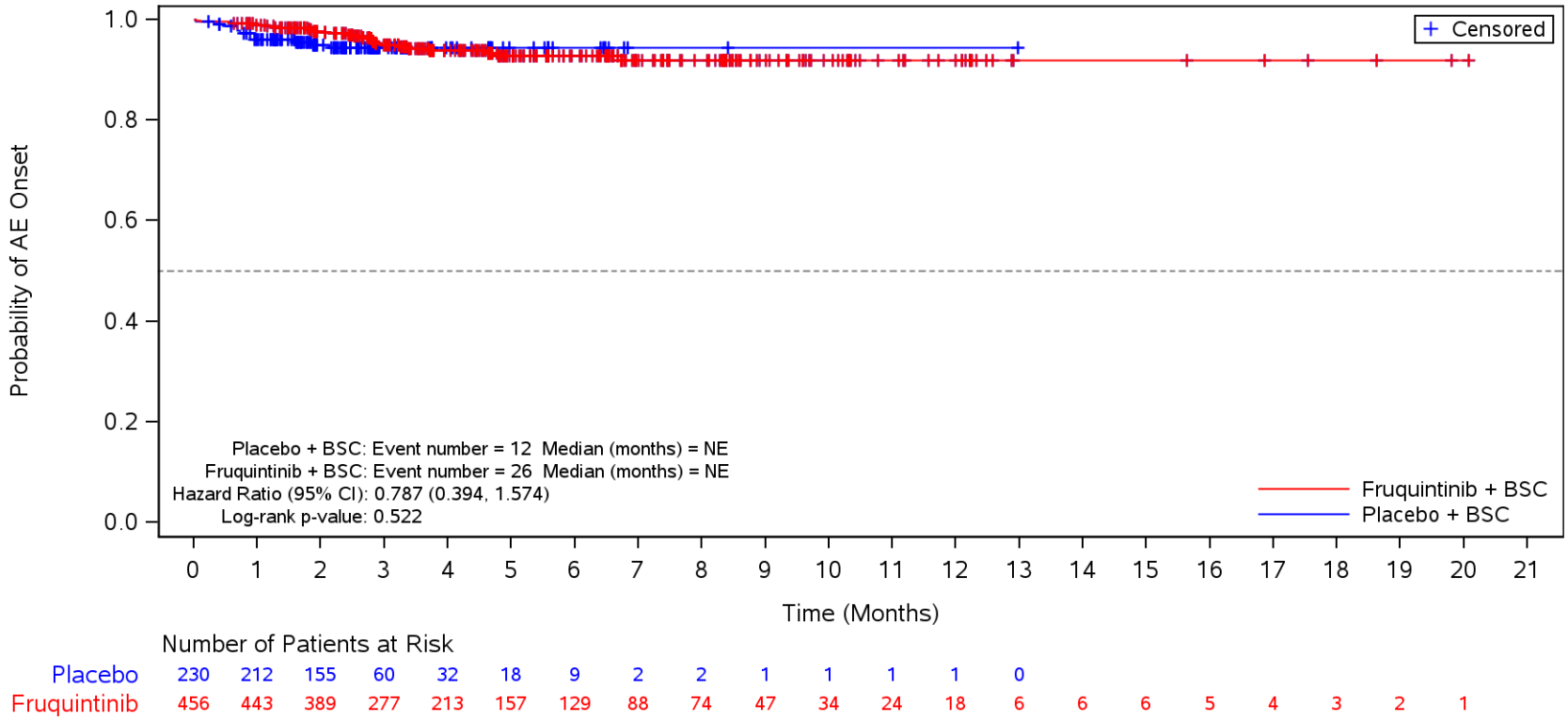
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders**



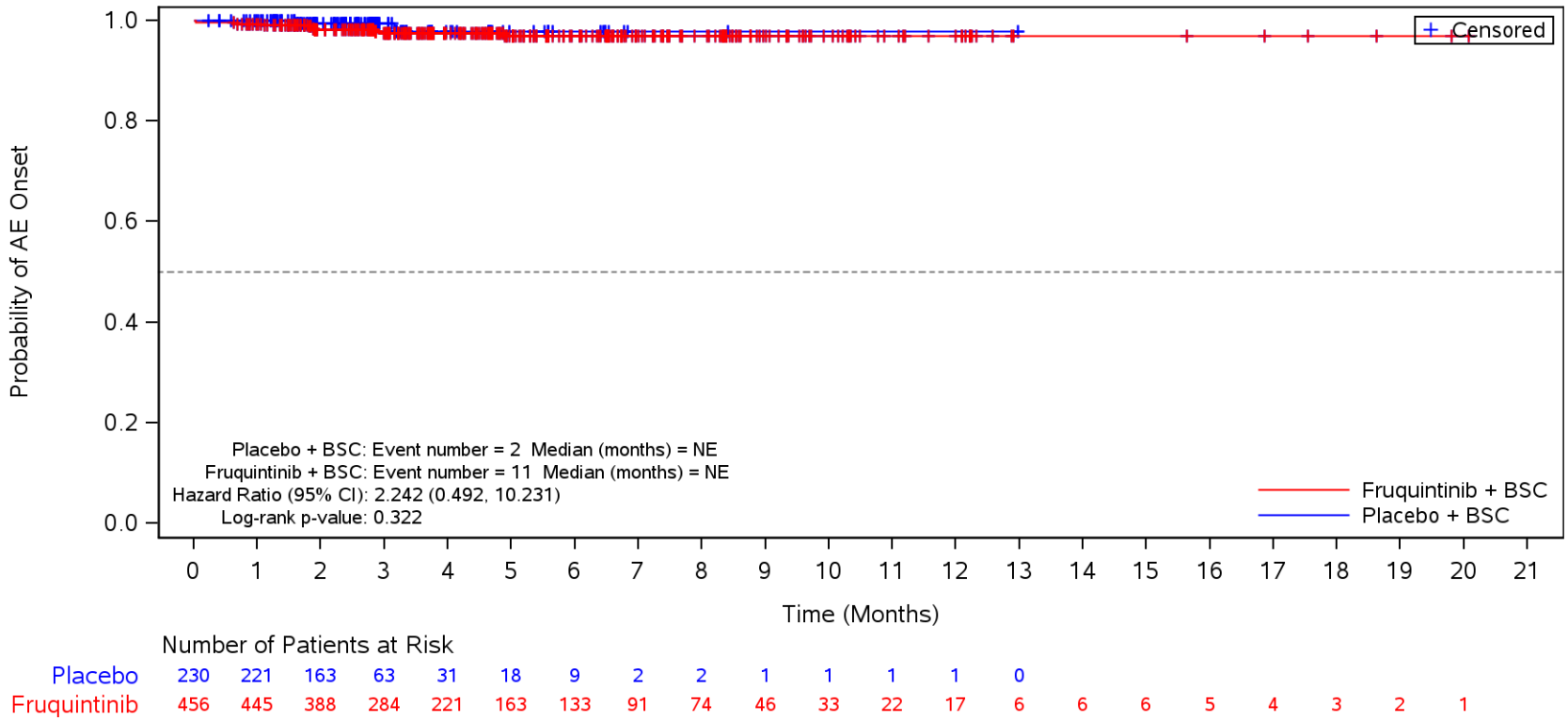
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Insomnia**



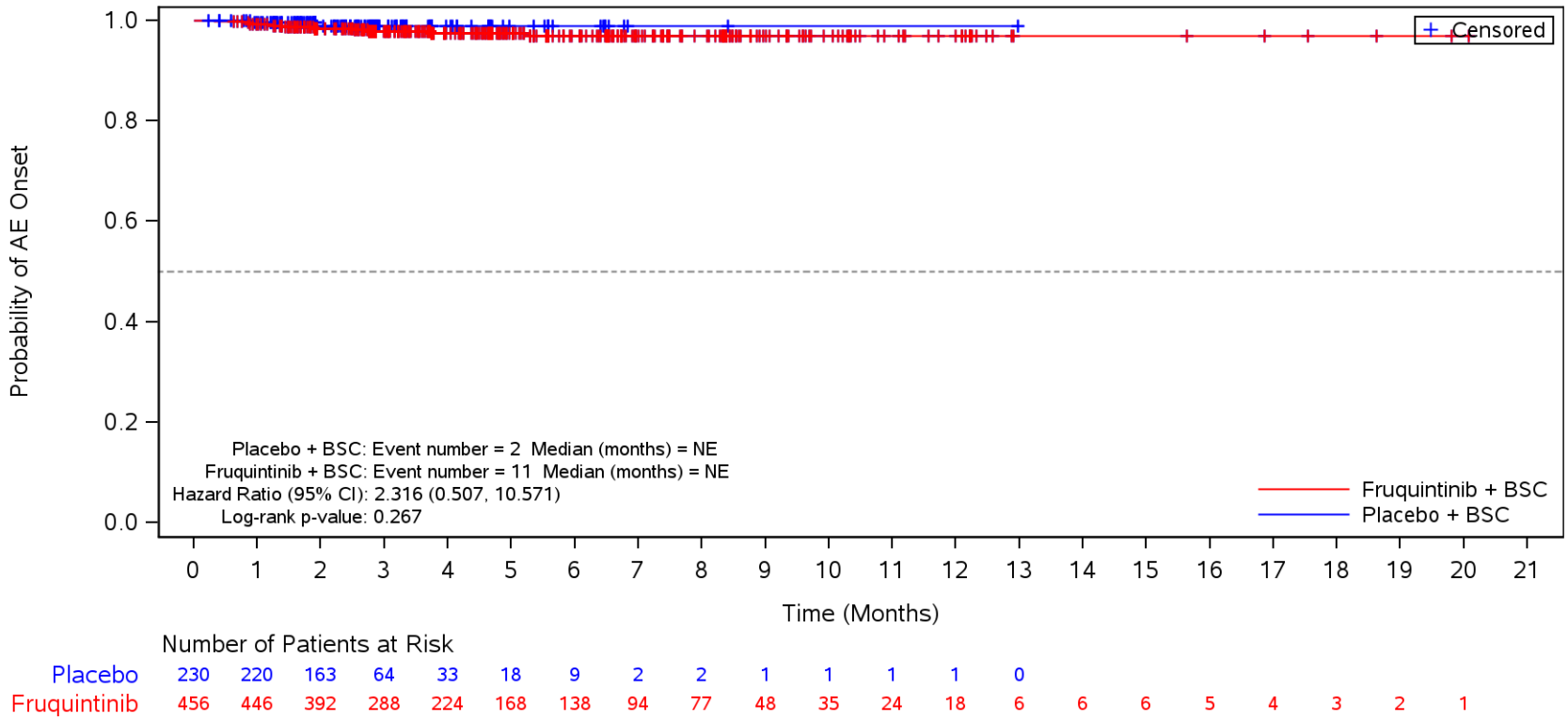
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Anxiety**



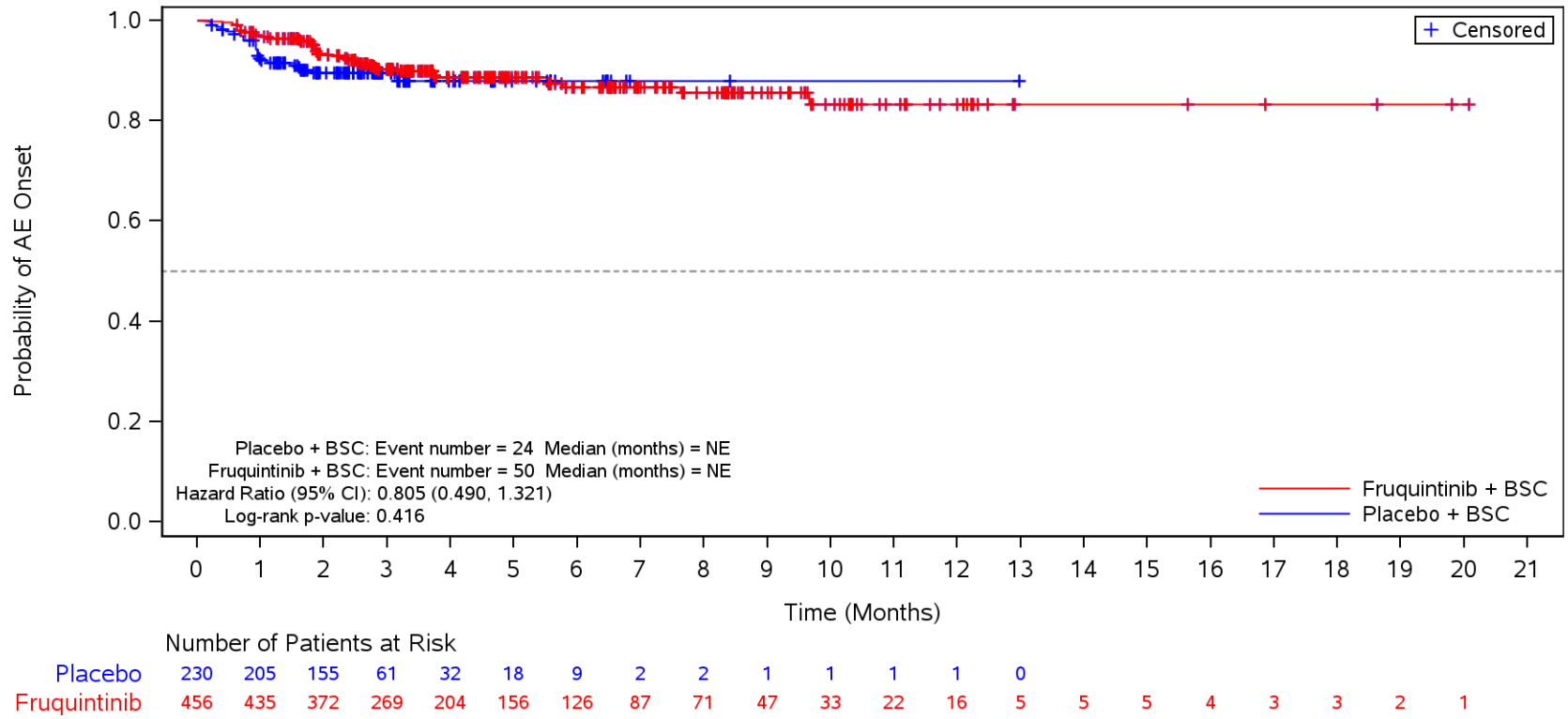
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Psychiatric disorders** and Preferred Term **Confusional state**



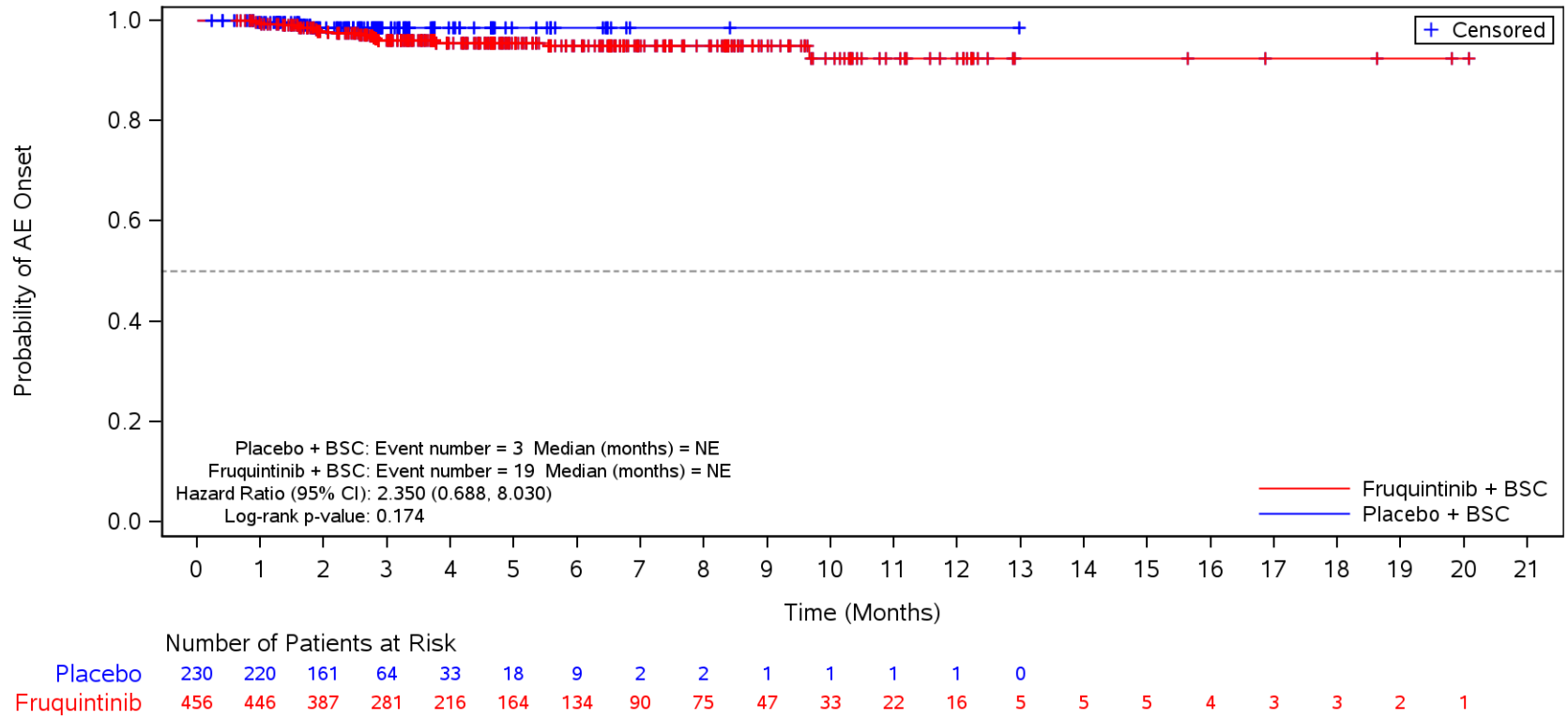
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders**



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE in SOC Term **Hepatobiliary disorders** and Preferred Term **Hypertransaminasaemia**



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

2.1.4 UE des NCI CTCAE-Grads ≥ 3 auf SOC-/PT-Level

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	44 (19.1)	91 (20.0)
Number of Subjects Censored, n (%)	186 (80.9)	365 (80.0)
Time to first TEAE (months)		
25% percentile (95% CI)	4.14 (2.76, NE)	11.04 (4.47, NE)
Median (95% CI)	NE (NE, NE)	NE (16.07, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.799 (0.187)
95% CI		(0.554, 1.154)
Log-rank p-value		0.245

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	80.7 (75.3, 86.0)	84.6 (81.2, 88.0)
6 months	74.9 (66.6, 83.1)	75.9 (71.2, 80.7)
9 months	74.9 (66.6, 83.1)	75.9 (71.2, 80.7)
12 months	74.9 (66.6, 83.1)	72.7 (65.2, 80.3)
18 months	NE (NE, NE)	54.3 (28.8, 79.9)
Median Follow-up Time (months)	2.83	3.60

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	28 (12.2)	27 (5.9)
Number of Subjects Censored, n (%)	202 (87.8)	429 (94.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (12.22, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.338 (0.278)
95% CI		(0.196, 0.583)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	87.2 (82.5, 91.9)	96.0 (94.2, 97.9)
6 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
9 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
12 months	83.6 (77.0, 90.3)	92.1 (88.9, 95.2)
18 months	NE (NE, NE)	85.9 (73.9, 97.9)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	9 (3.9)	35 (7.7)
Number of Subjects Censored, n (%)	221 (96.1)	421 (92.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	16.07 (16.07, NE)
Median (95% CI)	NE (NE, NE)	NE (16.07, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.598 (0.378)
95% CI		(0.761, 3.355)
Log-rank p-value		0.192

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.7 (92.9, 98.5)	93.4 (91.1, 95.8)
6 months	95.7 (92.9, 98.5)	91.2 (88.0, 94.3)
9 months	95.7 (92.9, 98.5)	91.2 (88.0, 94.3)
12 months	95.7 (92.9, 98.5)	87.4 (79.5, 95.2)
18 months	NE (NE, NE)	69.9 (38.6, 100.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	67 (14.7)
Number of Subjects Censored, n (%)	226 (98.3)	389 (85.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (10.35, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		8.524 (0.515)
95% CI		(3.105, 23.403)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.7 (97.1, 100.0)	85.6 (82.3, 88.8)
6 months	96.4 (91.8, 100.0)	84.4 (80.8, 88.0)
9 months	96.4 (91.8, 100.0)	84.4 (80.8, 88.0)
12 months	96.4 (91.8, 100.0)	81.0 (73.7, 88.4)
18 months	NE (NE, NE)	81.0 (73.7, 88.4)
Median Follow-up Time (months)	2.83	3.50

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders** and Preferred Term **Hypertension**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	62 (13.6)
Number of Subjects Censored, n (%)	228 (99.1)	394 (86.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (10.35, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		16.068 (0.719)
95% CI		(3.928, 65.730)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders** and Preferred Term **Hypertension**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.8, 100.0)	86.5 (83.3, 89.7)
6 months	99.1 (97.8, 100.0)	86.0 (82.6, 89.3)
9 months	99.1 (97.8, 100.0)	86.0 (82.6, 89.3)
12 months	99.1 (97.8, 100.0)	82.7 (75.5, 89.8)
18 months	NE (NE, NE)	82.7 (75.5, 89.8)
Median Follow-up Time (months)	2.83	3.53

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Skin and subcutaneous tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	31 (6.8)
Number of Subjects Censored, n (%)	229 (99.6)	425 (93.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.14 (13.14, NE)
Median (95% CI)	NE (NE, NE)	NE (13.14, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		11.778 (1.019)
95% CI		(1.597, 86.838)
Log-rank p-value		0.002

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Skin and subcutaneous tissue disorders**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	94.9 (92.8, 97.0)
6 months	99.6 (98.7, 100.0)	90.8 (87.2, 94.4)
9 months	99.6 (98.7, 100.0)	89.7 (85.5, 93.9)
12 months	99.6 (98.7, 100.0)	89.7 (85.5, 93.9)
18 months	NE (NE, NE)	67.3 (29.1, 100.0)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Palmar-plantar erythrodysaesthesia syndrome**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	29 (6.4)
Number of Subjects Censored, n (%)	230 (100.0)	427 (93.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.6.5.3A
Summary of Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Skin and subcutaneous tissue disorders** and Preferred Term **Palmar-plantar erythrodysaesthesia syndrome**

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	95.1 (93.0, 97.1)
6 months	100.0 (100.0, 100.0)	91.0 (87.5, 94.6)
9 months	100.0 (100.0, 100.0)	89.9 (85.7, 94.1)
12 months	100.0 (100.0, 100.0)	89.9 (85.7, 94.1)
18 months	NE (NE, NE)	89.9 (85.7, 94.1)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

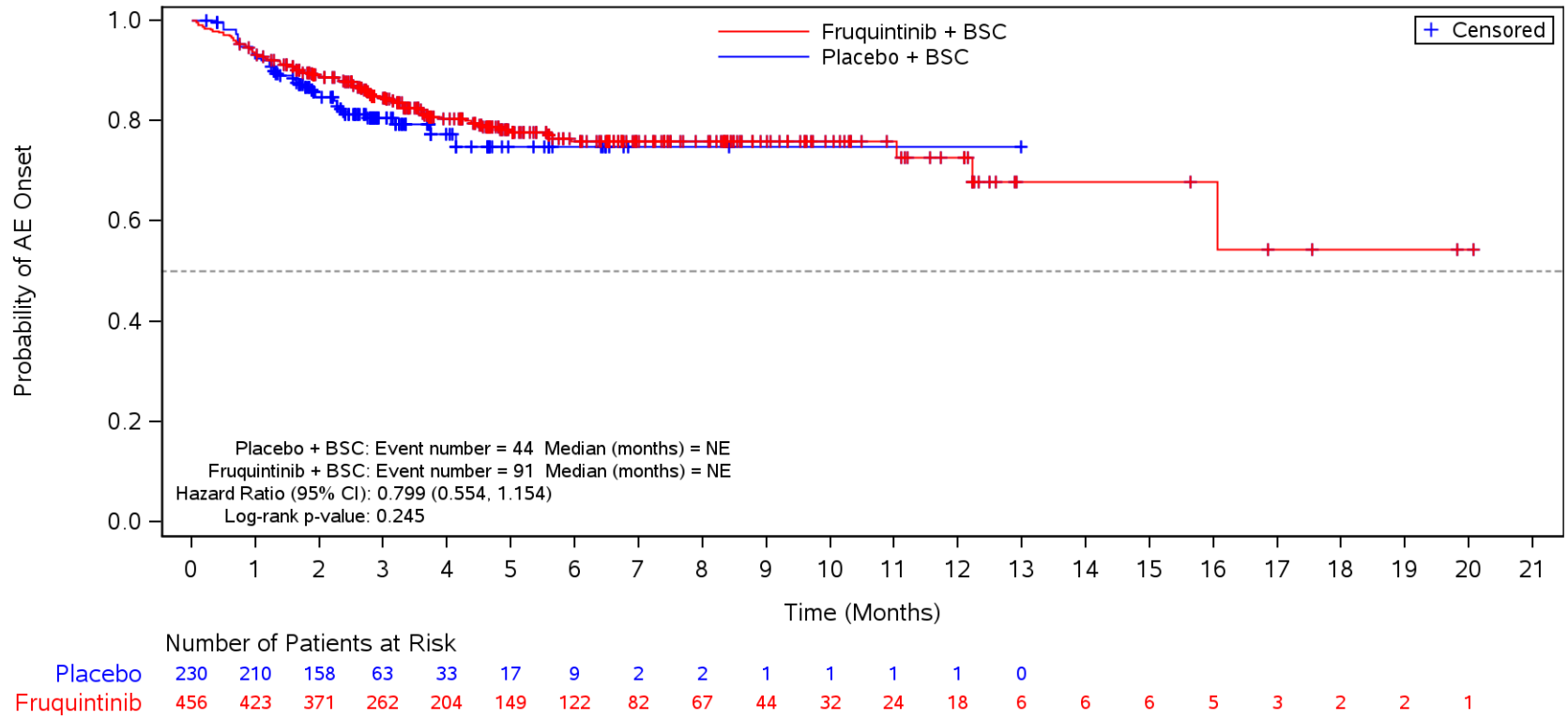
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

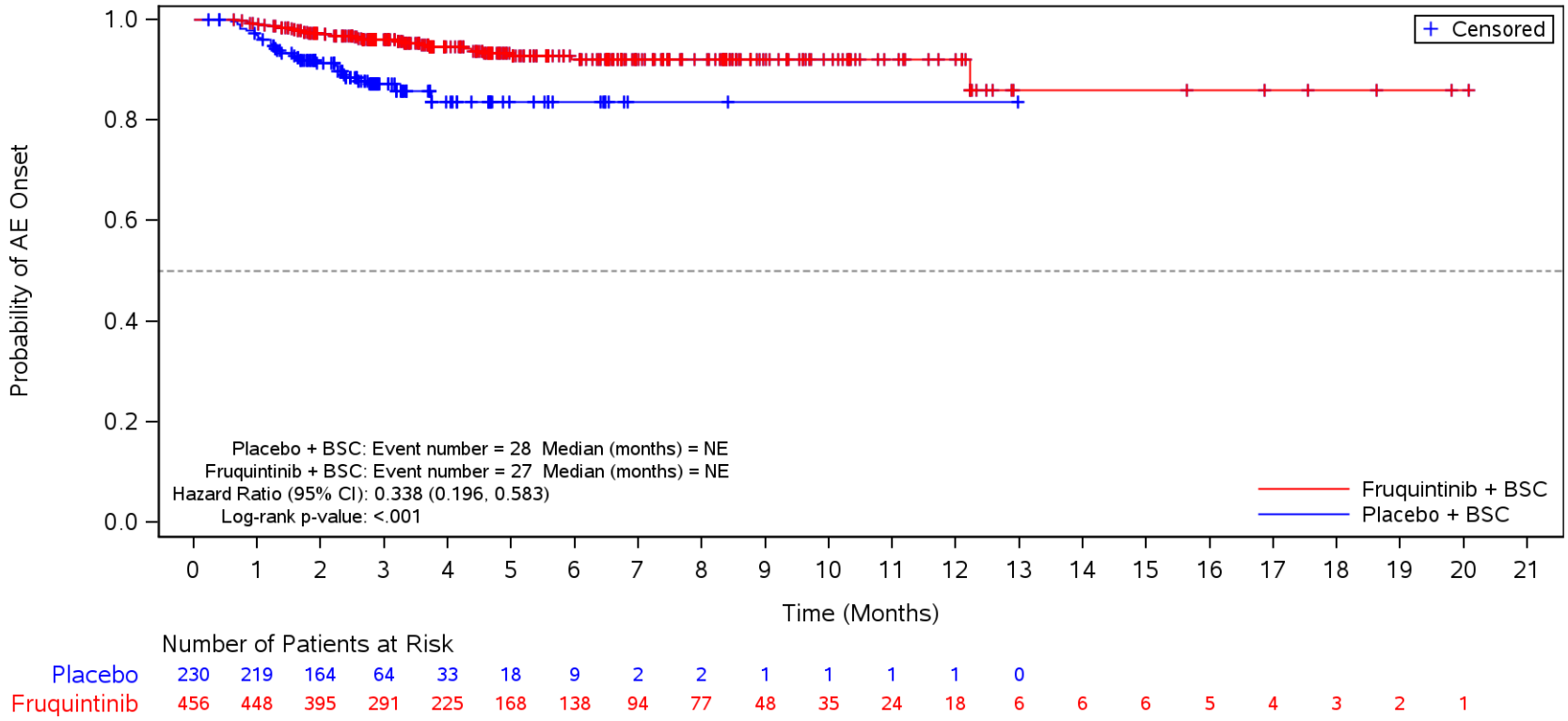
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions**



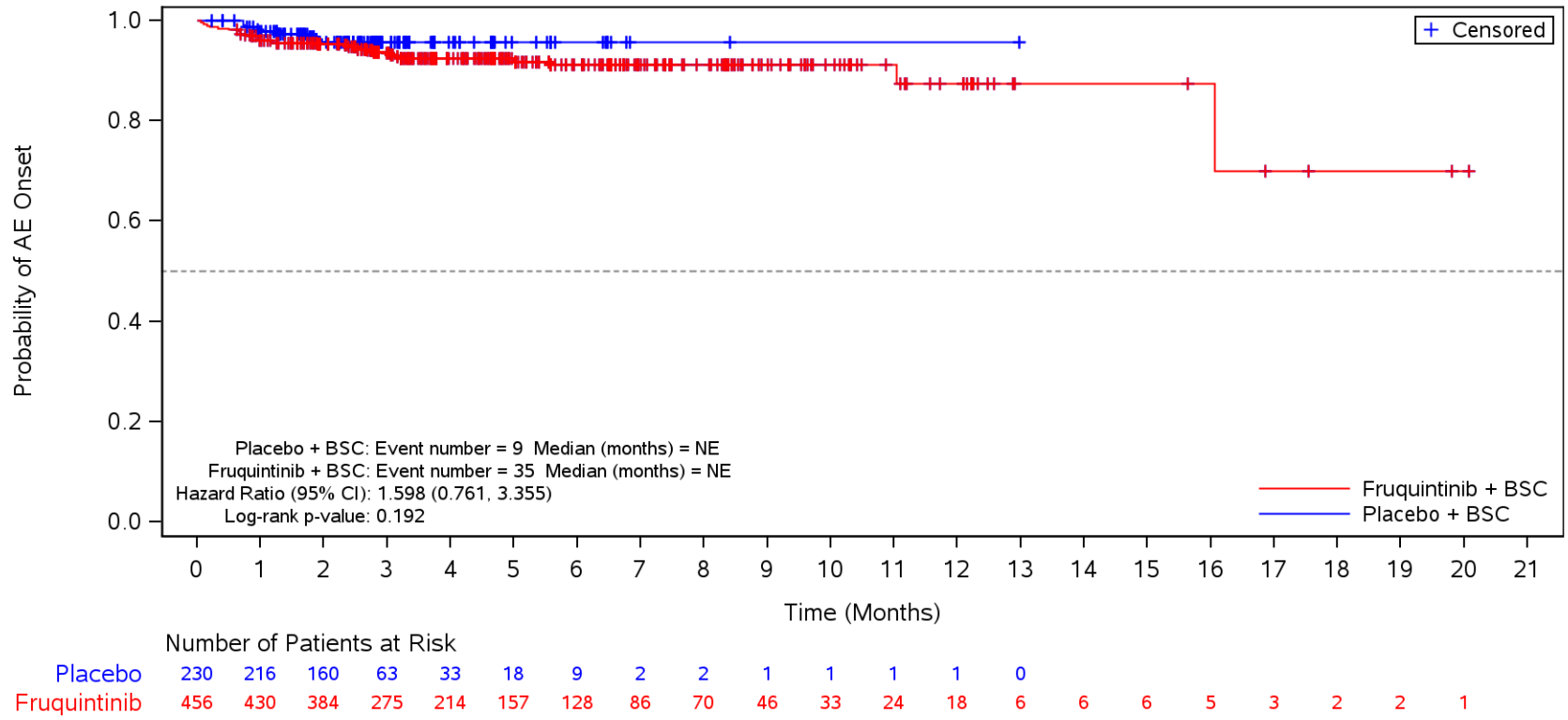
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Disease progression**



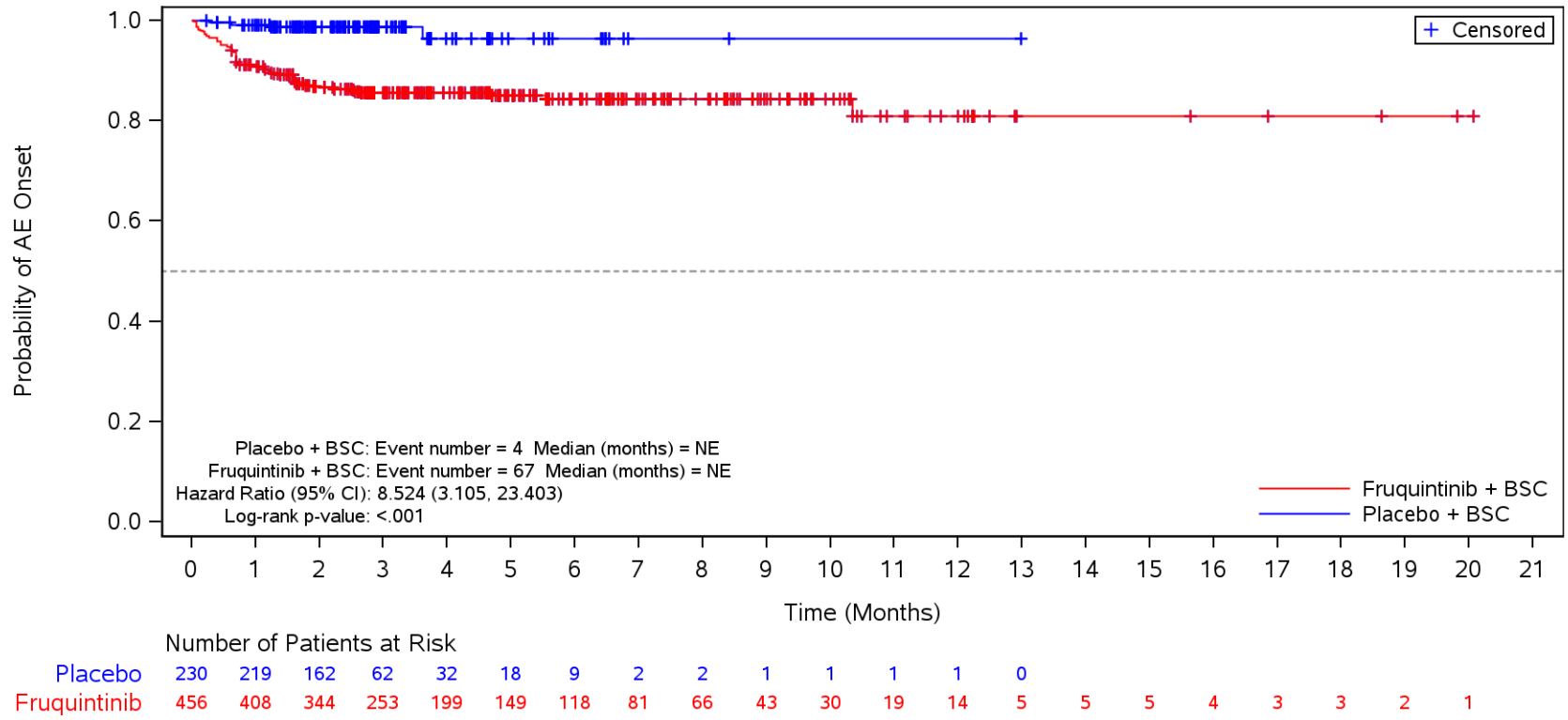
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **General disorders and administration site conditions** and Preferred Term **Asthenia**



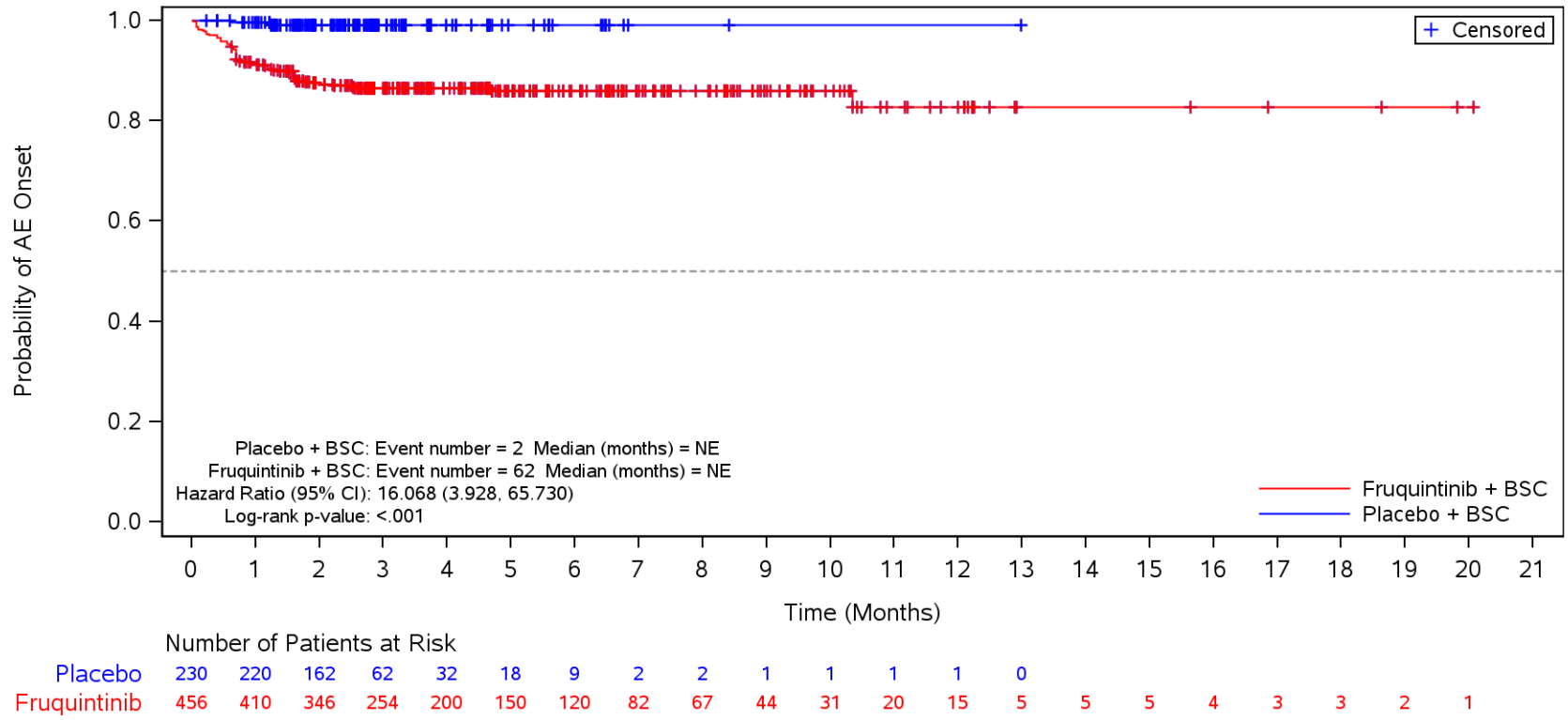
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders**



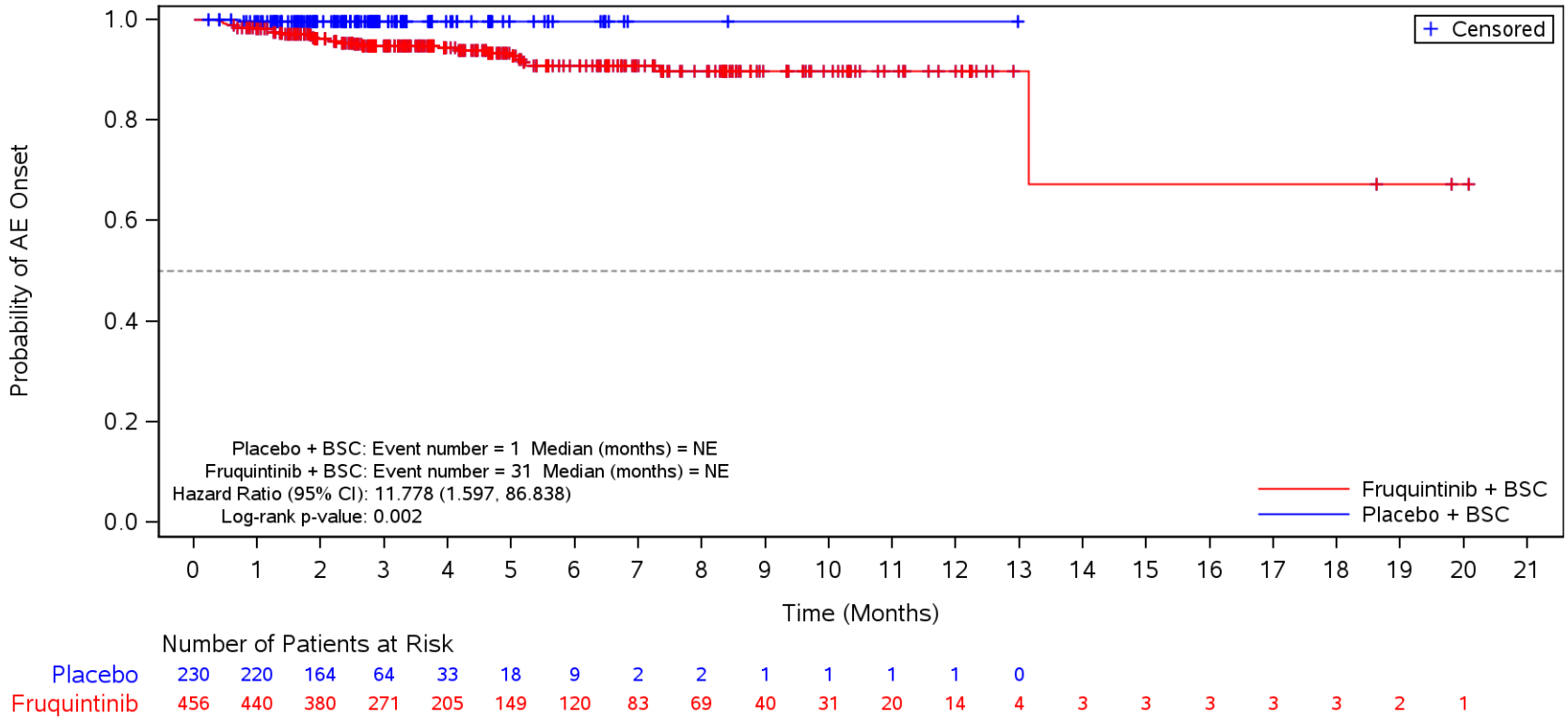
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Vascular disorders** and Preferred Term **Hypertension**

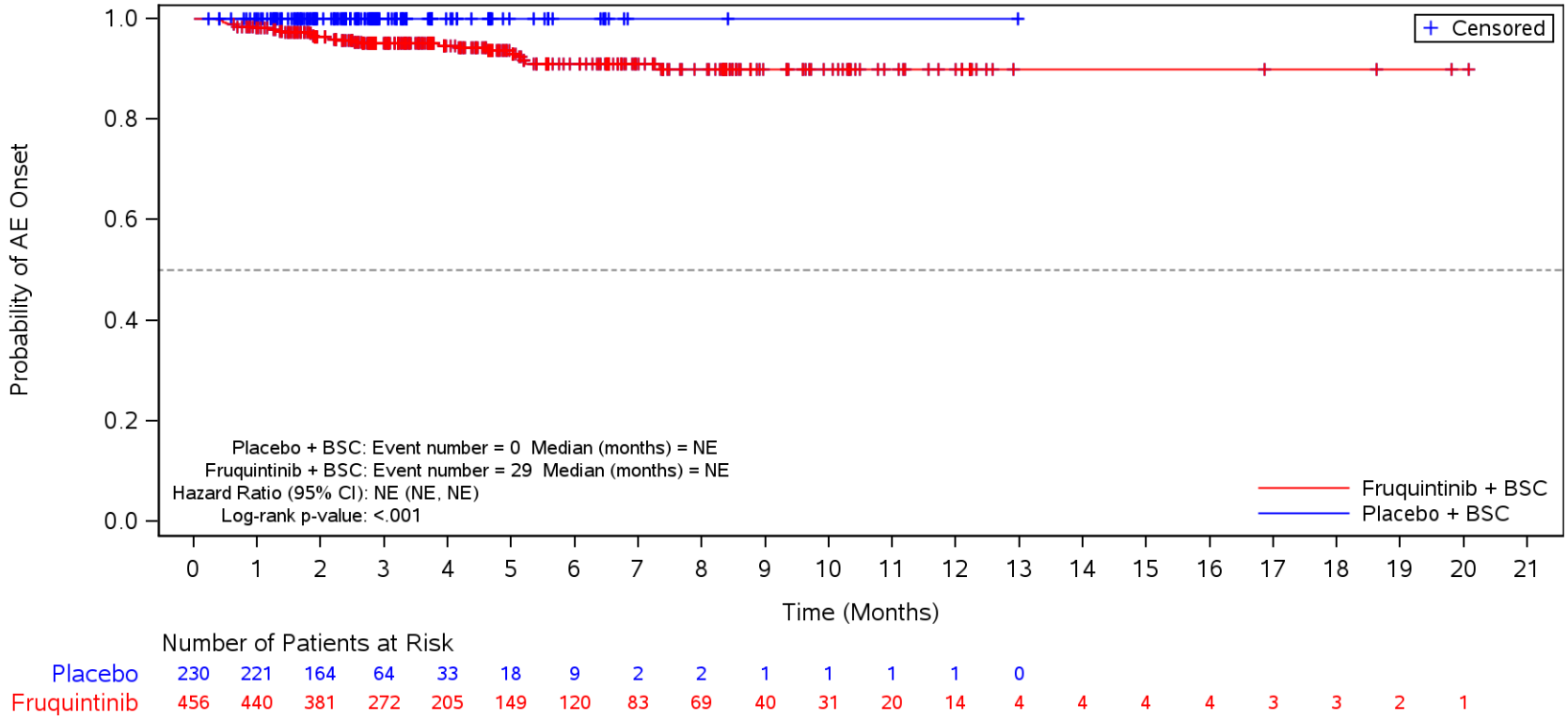


BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.6.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
TEAE ≥ CTCAE Grade 3 in SOC Term **Skin and subcutaneous tissue disorders**



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.


Probability of AE Onset
1.0
0.8
0.6
0.4
0.2
0.0
Censored
Placebo + BSC: Event number = 0 Median (months) = NE
Fruquintinib + BSC: Event number = 29 Median (months) = NE
Hazard Ratio (95% CI): NE (NE, NE)
Log-rank p-value: <.001
Fruquintinib + BSC
Placebo + BSC
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Time (Months)
Number of Patients at Risk
Placebo 230 221 164 64 33 18 9 2 2 1 1 1 1 0
Fruquintinib 456 440 381 272 205 149 120 83 69 40 31 20 14 4 4 4 4 3 3 2 1

2.1.5 Schwerwiegende UE auf SOC-/PT-Level

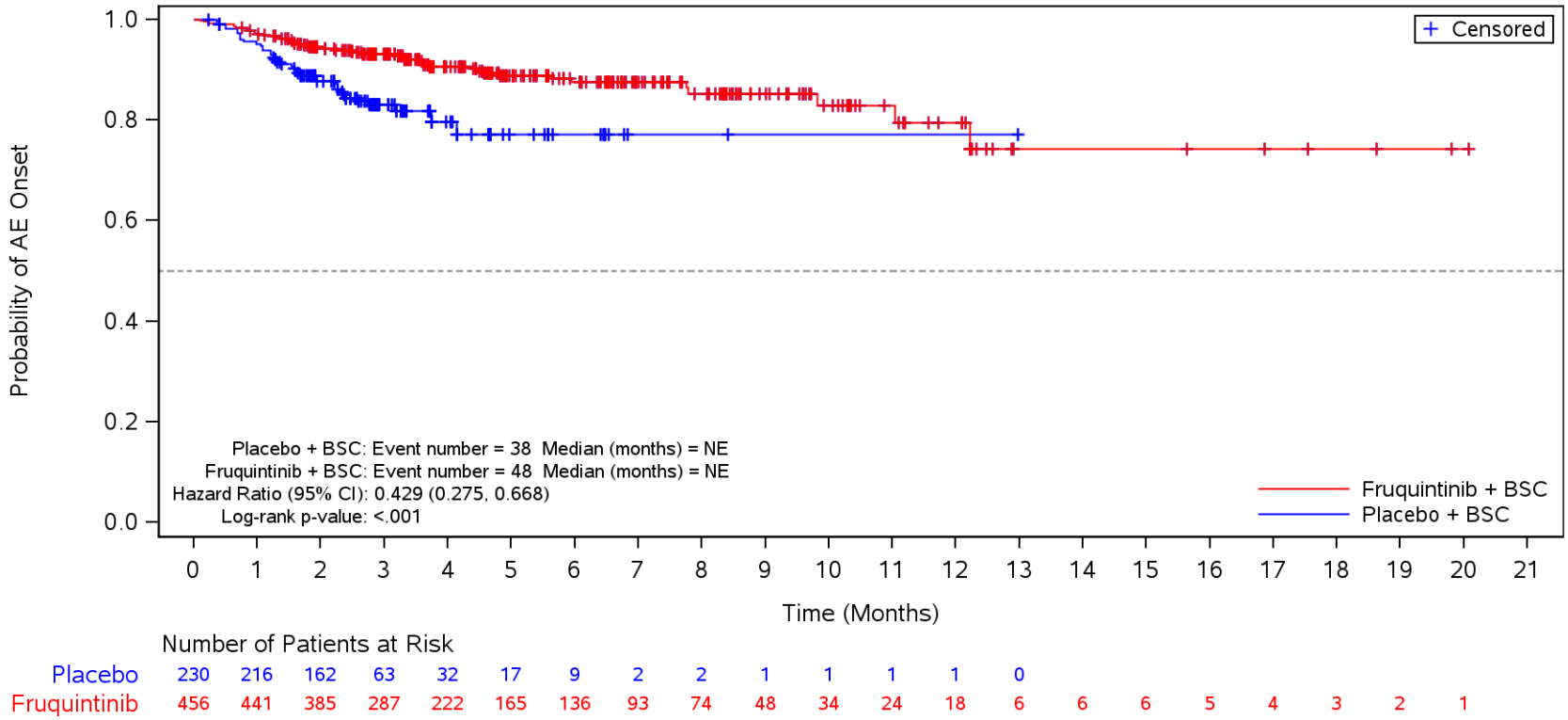
Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	38 (16.5)	48 (10.5)
Number of Subjects Censored, n (%)	192 (83.5)	408 (89.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (3.75, NE)	12.22 (11.04, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.429 (0.226)
95% CI		(0.275, 0.668)
Log-rank p-value		<.001

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	83.2 (78.0, 88.3)	93.2 (90.8, 95.5)
6 months	77.1 (68.7, 85.5)	87.6 (83.9, 91.4)
9 months	77.1 (68.7, 85.5)	85.3 (80.5, 90.1)
12 months	77.1 (68.7, 85.5)	79.5 (70.4, 88.6)
18 months	NE (NE, NE)	74.2 (61.0, 87.4)
Median Follow-up Time (months)	2.83	3.78

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	28 (12.2)	26 (5.7)
Number of Subjects Censored, n (%)	202 (87.8)	430 (94.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (12.22, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.330 (0.280)
95% CI		(0.191, 0.572)
Log-rank p-value		<.001

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	87.2 (82.5, 91.8)	96.0 (94.2, 97.9)
6 months	83.6 (77.0, 90.3)	92.5 (89.4, 95.5)
9 months	83.6 (77.0, 90.3)	92.5 (89.4, 95.5)
12 months	83.6 (77.0, 90.3)	92.5 (89.4, 95.5)
18 months	NE (NE, NE)	86.3 (74.3, 98.3)
Median Follow-up Time (months)	2.83	3.94

Figure 35.1.1.6.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE by SOC/PT
Safety Population
Serious TEAE in SOC Term **General disorders and administration site conditions**



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

2.1.6 AESI

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	123 (27.0)
Number of Subjects Censored, n (%)	226 (98.3)	333 (73.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	3.81 (2.63, 5.52)
Median (95% CI)	NE (NE, NE)	NE (9.33, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		13.363 (0.509)
95% CI		(4.926, 36.249)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.5 (96.8, 100.0)	76.9 (72.8, 80.9)
6 months	96.2 (91.5, 100.0)	66.8 (61.0, 72.5)
9 months	96.2 (91.5, 100.0)	60.3 (52.8, 67.8)
12 months	96.2 (91.5, 100.0)	57.6 (48.7, 66.4)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.83	2.84

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	80 (17.5)
Number of Subjects Censored, n (%)	218 (94.8)	376 (82.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.60 (5.78, NE)
Median (95% CI)	NE (NE, NE)	NE (13.60, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.60, NE)
Min, Max	0.2*, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.856 (0.312)
95% CI		(1.550, 5.260)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.4 (91.4, 97.5)	84.3 (80.8, 87.8)
6 months	94.4 (91.4, 97.5)	79.7 (75.4, 84.1)
9 months	94.4 (91.4, 97.5)	77.0 (71.4, 82.7)
12 months	94.4 (91.4, 97.5)	77.0 (71.4, 82.7)
18 months	NE (NE, NE)	57.8 (24.8, 90.7)
Median Follow-up Time (months)	2.79	3.33

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	20 (8.7)	175 (38.4)
Number of Subjects Censored, n (%)	210 (91.3)	281 (61.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	0.95 (0.69, 1.58)
Median (95% CI)	NE (NE, NE)	NE (7.39, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.847 (0.237)
95% CI		(3.049, 7.706)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	90.5 (86.5, 94.5)	62.4 (57.8, 66.9)
6 months	90.5 (86.5, 94.5)	59.9 (55.1, 64.8)
9 months	NE (NE, NE)	55.4 (49.1, 61.6)
12 months	NE (NE, NE)	55.4 (49.1, 61.6)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.79	2.74

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	22 (9.6)	65 (14.3)
Number of Subjects Censored, n (%)	208 (90.4)	391 (85.7)
Time to first TEAE (months)		
25% percentile (95% CI)	5.72 (4.57, NE)	NE (9.20, NE)
Median (95% CI)	NE (5.72, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.175 (0.251)
95% CI		(0.719, 1.922)
Log-rank p-value		0.507

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	91.1 (87.3, 95.0)	88.0 (85.0, 91.1)
6 months	74.6 (53.6, 95.6)	82.8 (78.6, 87.1)
9 months	74.6 (53.6, 95.6)	82.1 (77.6, 86.5)
12 months	74.6 (53.6, 95.6)	79.7 (73.5, 86.0)
18 months	NE (NE, NE)	79.7 (73.5, 86.0)
Median Follow-up Time (months)	2.79	3.40

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	16 (3.5)
Number of Subjects Censored, n (%)	229 (99.6)	440 (96.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.711 (1.044)
95% CI		(0.608, 36.474)
Log-rank p-value		0.094

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.4 (98.2, 100.0)	97.9 (96.5, 99.3)
6 months	99.4 (98.2, 100.0)	95.1 (92.3, 97.9)
9 months	99.4 (98.2, 100.0)	92.1 (87.1, 97.1)
12 months	99.4 (98.2, 100.0)	92.1 (87.1, 97.1)
18 months	NE (NE, NE)	92.1 (87.1, 97.1)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	5 (2.2)	21 (4.6)
Number of Subjects Censored, n (%)	225 (97.8)	435 (95.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.277 (0.513)
95% CI		(0.467, 3.489)
Log-rank p-value		0.584

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.1 (96.2, 99.9)	97.4 (95.9, 98.9)
6 months	95.8 (91.1, 100.0)	93.3 (90.0, 96.5)
9 months	95.8 (91.1, 100.0)	92.1 (88.2, 96.0)
12 months	95.8 (91.1, 100.0)	89.6 (83.3, 95.8)
18 months	NE (NE, NE)	89.6 (83.3, 95.8)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	44 (19.1)	113 (24.8)
Number of Subjects Censored, n (%)	186 (80.9)	343 (75.2)
Time to first TEAE (months)		
25% percentile (95% CI)	5.59 (3.15, NE)	4.07 (2.83, 6.67)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 8.4*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.050 (0.180)
95% CI		(0.737, 1.495)
Log-rank p-value		0.777

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	81.0 (75.8, 86.2)	78.6 (74.7, 82.5)
6 months	74.5 (63.6, 85.4)	71.9 (67.0, 76.7)
9 months	NE (NE, NE)	68.6 (63.0, 74.3)
12 months	NE (NE, NE)	66.6 (59.9, 73.3)
18 months	NE (NE, NE)	66.6 (59.9, 73.3)
Median Follow-up Time (months)	2.79	3.27

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	6 (2.6)	5 (1.1)
Number of Subjects Censored, n (%)	224 (97.4)	451 (98.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.320 (0.621)
95% CI		(0.095, 1.081)
Log-rank p-value		0.062

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	97.8 (95.8, 99.7)	99.1 (98.1, 100.0)
6 months	95.6 (90.9, 100.0)	98.7 (97.5, 99.9)
9 months	95.6 (90.9, 100.0)	98.7 (97.5, 99.9)
12 months	95.6 (90.9, 100.0)	98.7 (97.5, 99.9)
18 months	NE (NE, NE)	98.7 (97.5, 99.9)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	27 (11.7)	157 (34.4)
Number of Subjects Censored, n (%)	203 (88.3)	299 (65.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	1.58 (0.99, 1.84)
Median (95% CI)	NE (NE, NE)	13.14 (13.14, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.994 (0.209)
95% CI		(1.987, 4.512)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	88.3 (84.1, 92.5)	67.4 (63.0, 71.8)
6 months	85.8 (79.6, 92.1)	62.3 (57.2, 67.5)
9 months	85.8 (79.6, 92.1)	60.2 (54.4, 66.0)
12 months	85.8 (79.6, 92.1)	60.2 (54.4, 66.0)
18 months	NE (NE, NE)	45.1 (19.2, 71.0)
Median Follow-up Time (months)	2.78	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	29 (12.6)	96 (21.1)
Number of Subjects Censored, n (%)	201 (87.4)	360 (78.9)
Time to first TEAE (months)		
25% percentile (95% CI)	5.78 (4.34, NE)	5.91 (4.63, 7.69)
Median (95% CI)	NE (5.78, NE)	17.48 (11.53, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (17.48, NE)
Min, Max	0.0, 13.0*	0.1, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.153 (0.219)
95% CI		(0.751, 1.769)
Log-rank p-value		0.438

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.1.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	88.3 (83.9, 92.6)	84.5 (81.0, 88.0)
6 months	70.3 (49.9, 90.6)	74.7 (69.4, 80.0)
9 months	70.3 (49.9, 90.6)	65.2 (57.6, 72.8)
12 months	70.3 (49.9, 90.6)	60.9 (50.0, 71.7)
18 months	NE (NE, NE)	45.6 (18.6, 72.7)
Median Follow-up Time (months)	2.79	3.30

* indicates censored value.

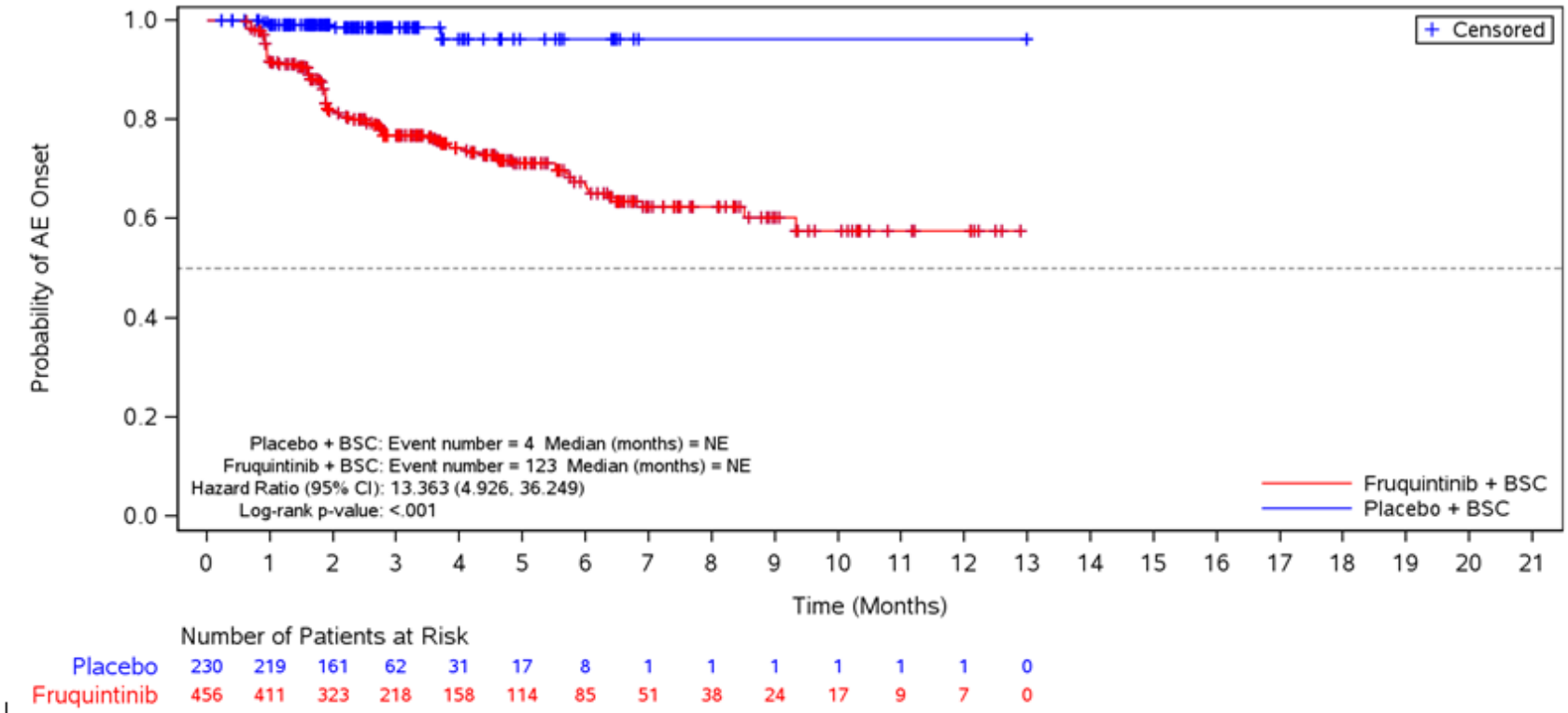
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

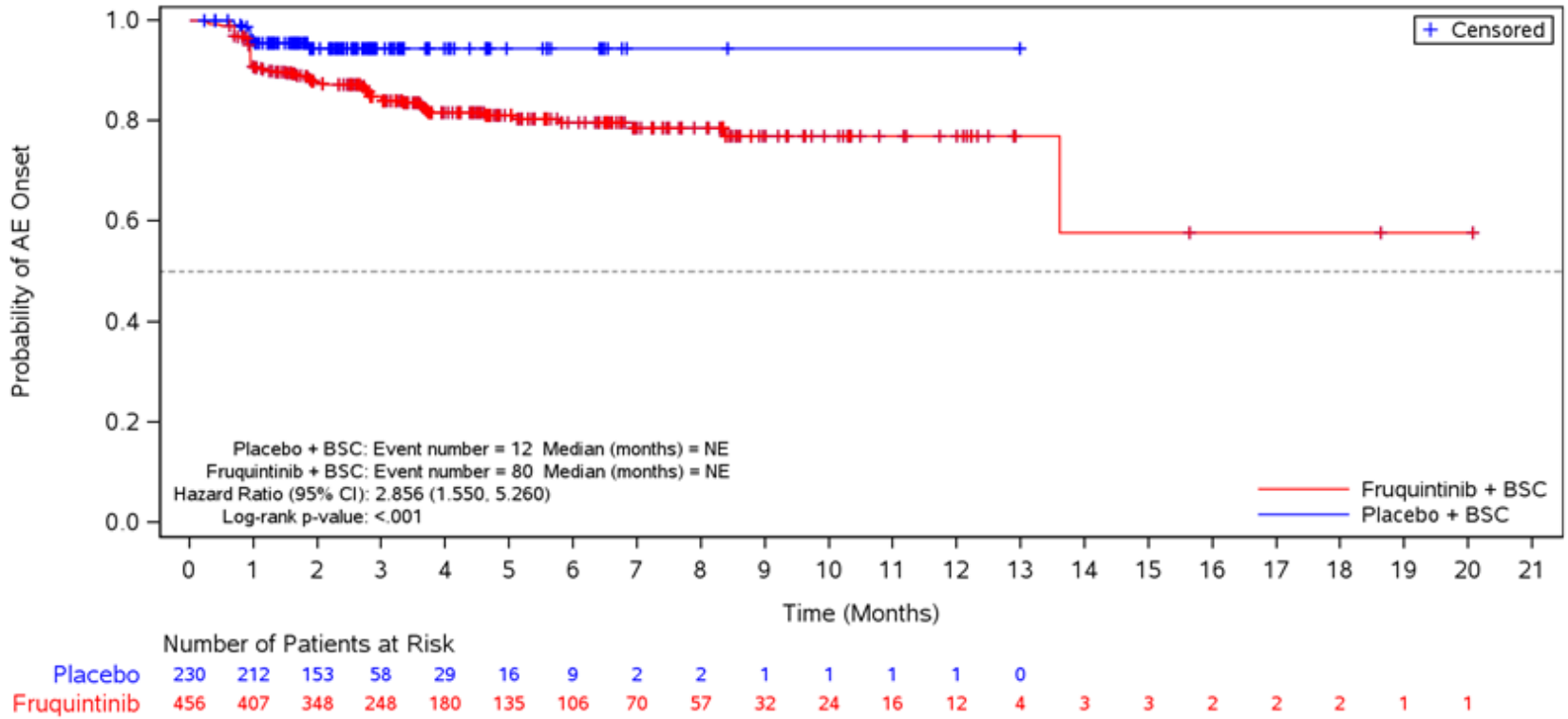
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE



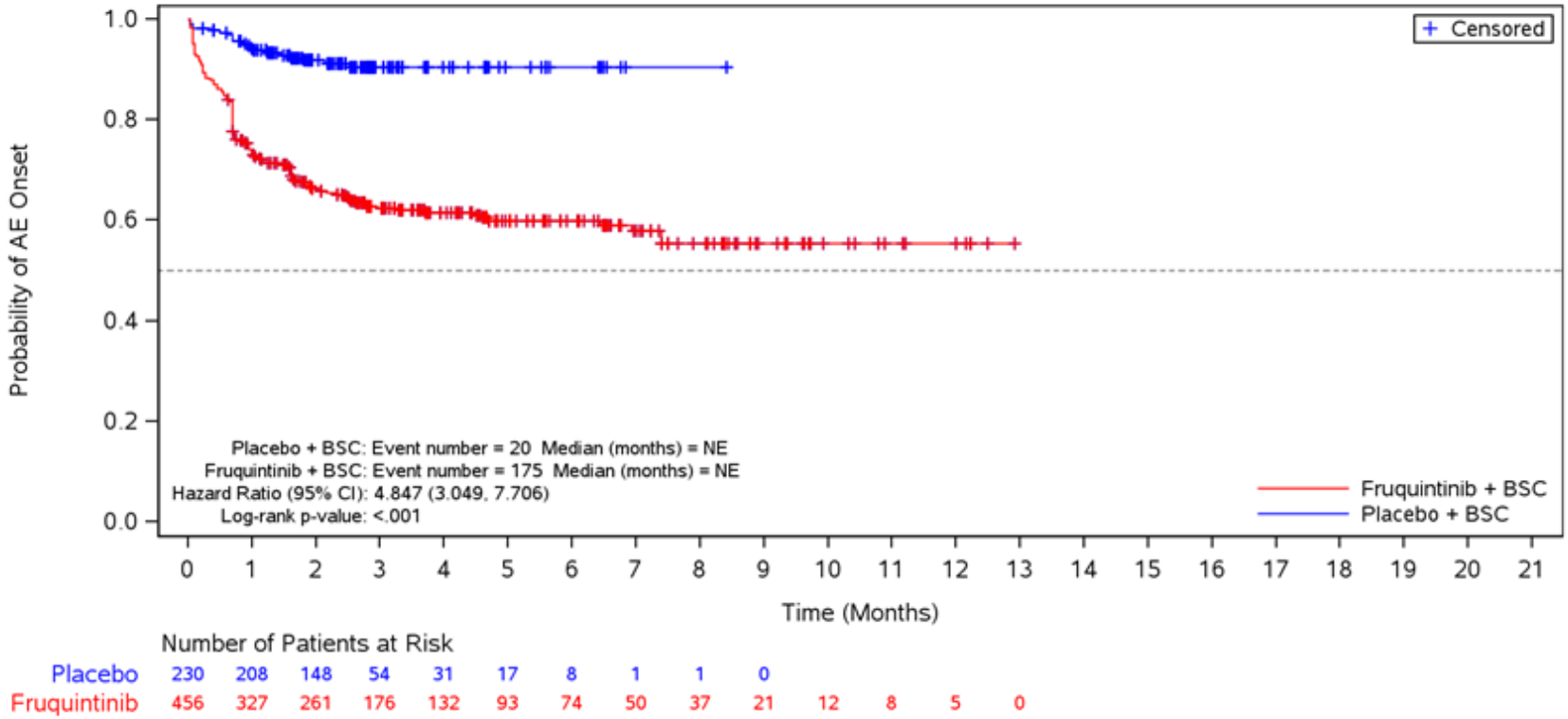
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE



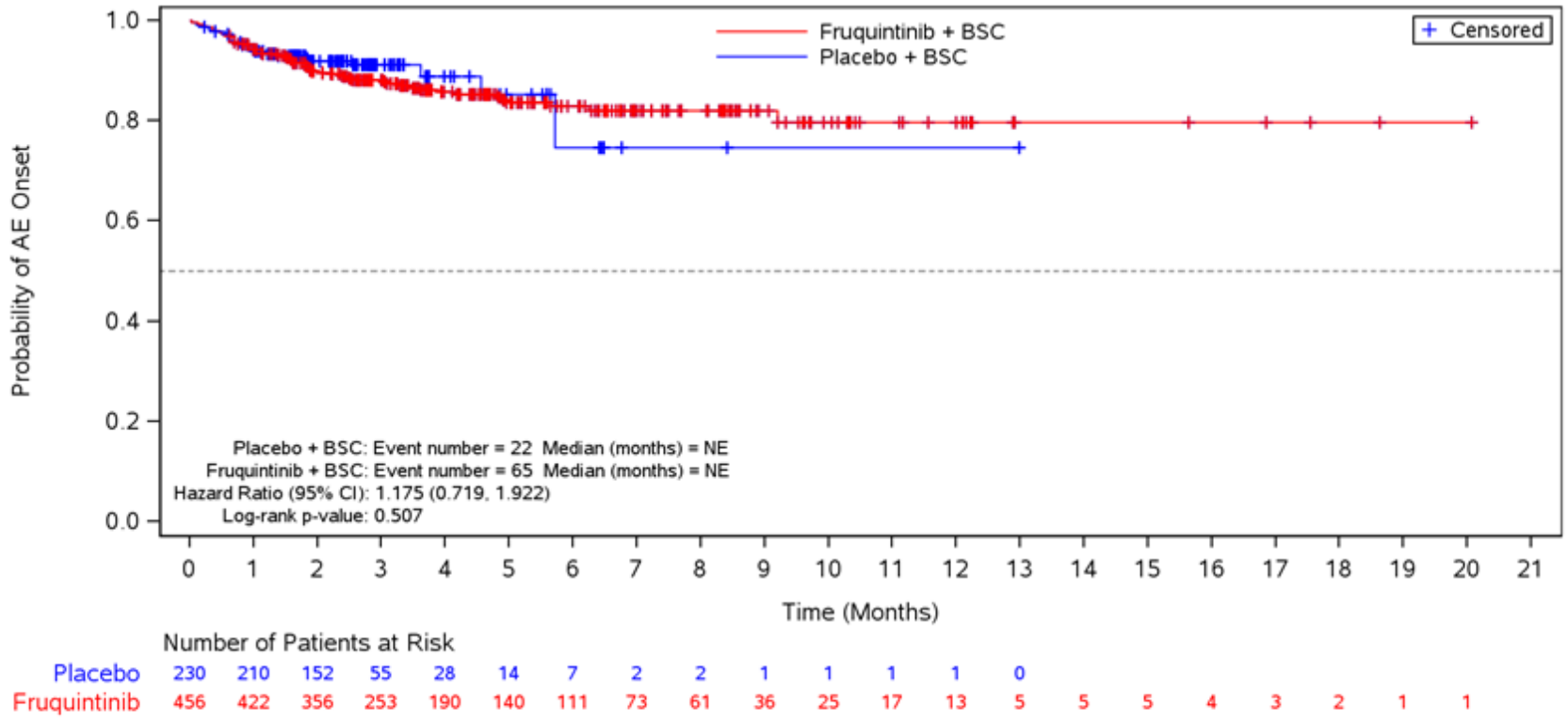
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE



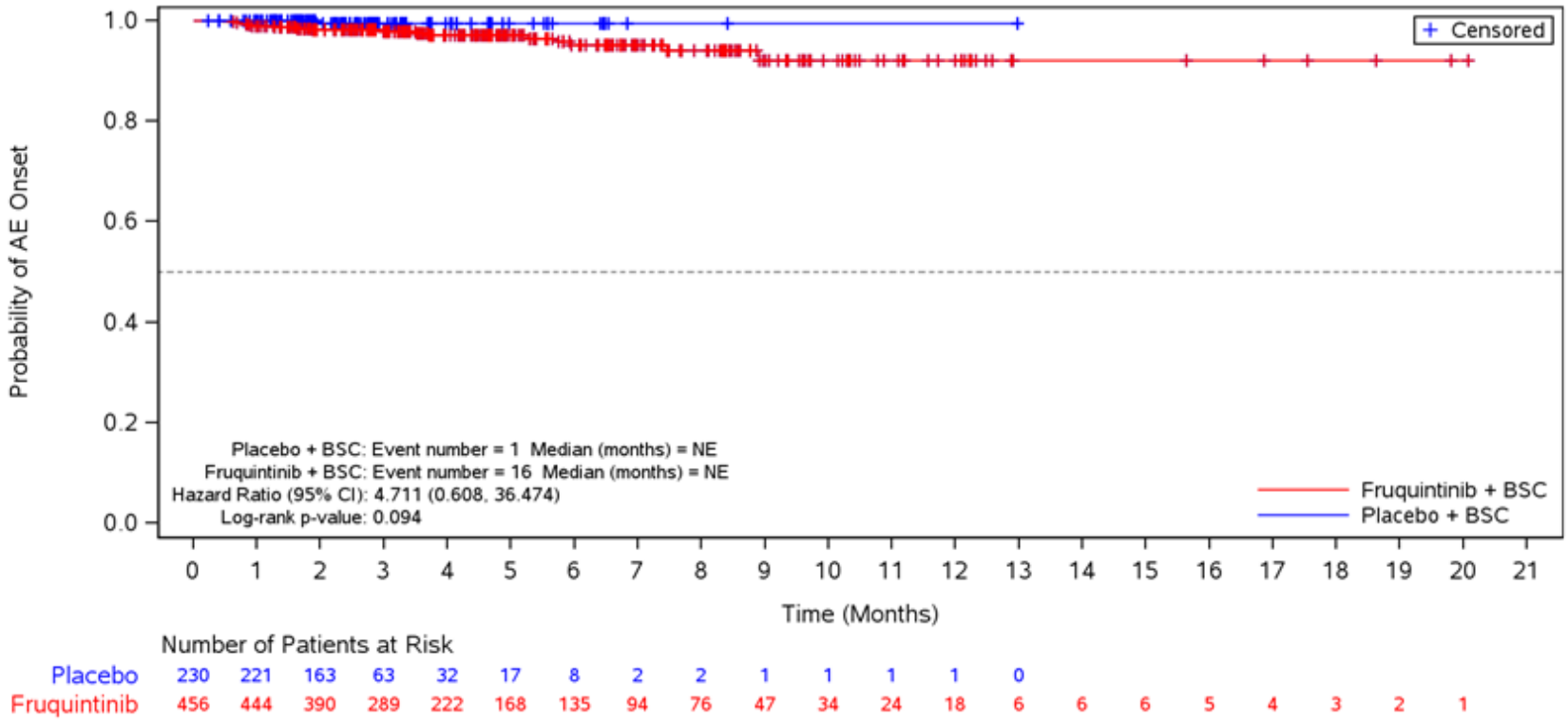
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE



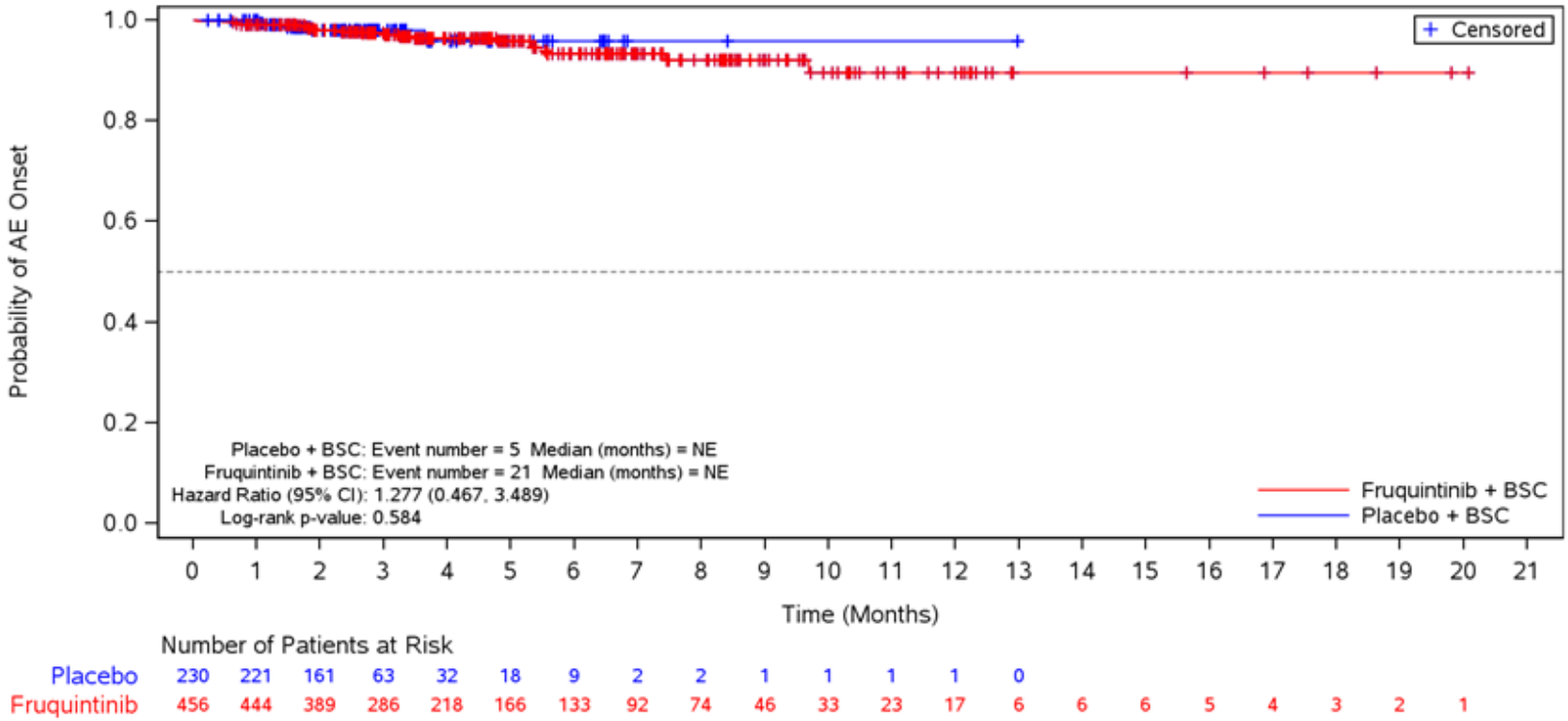
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE



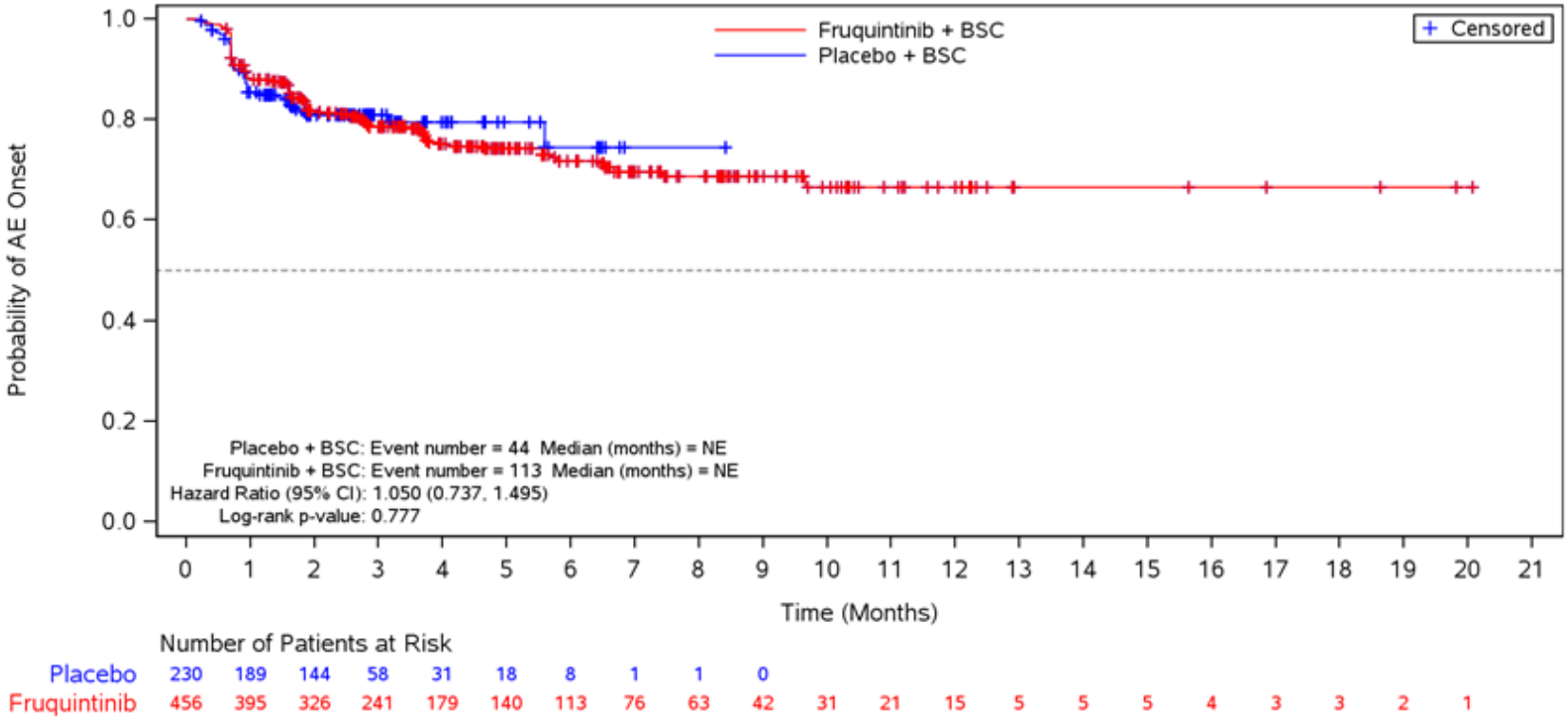
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE



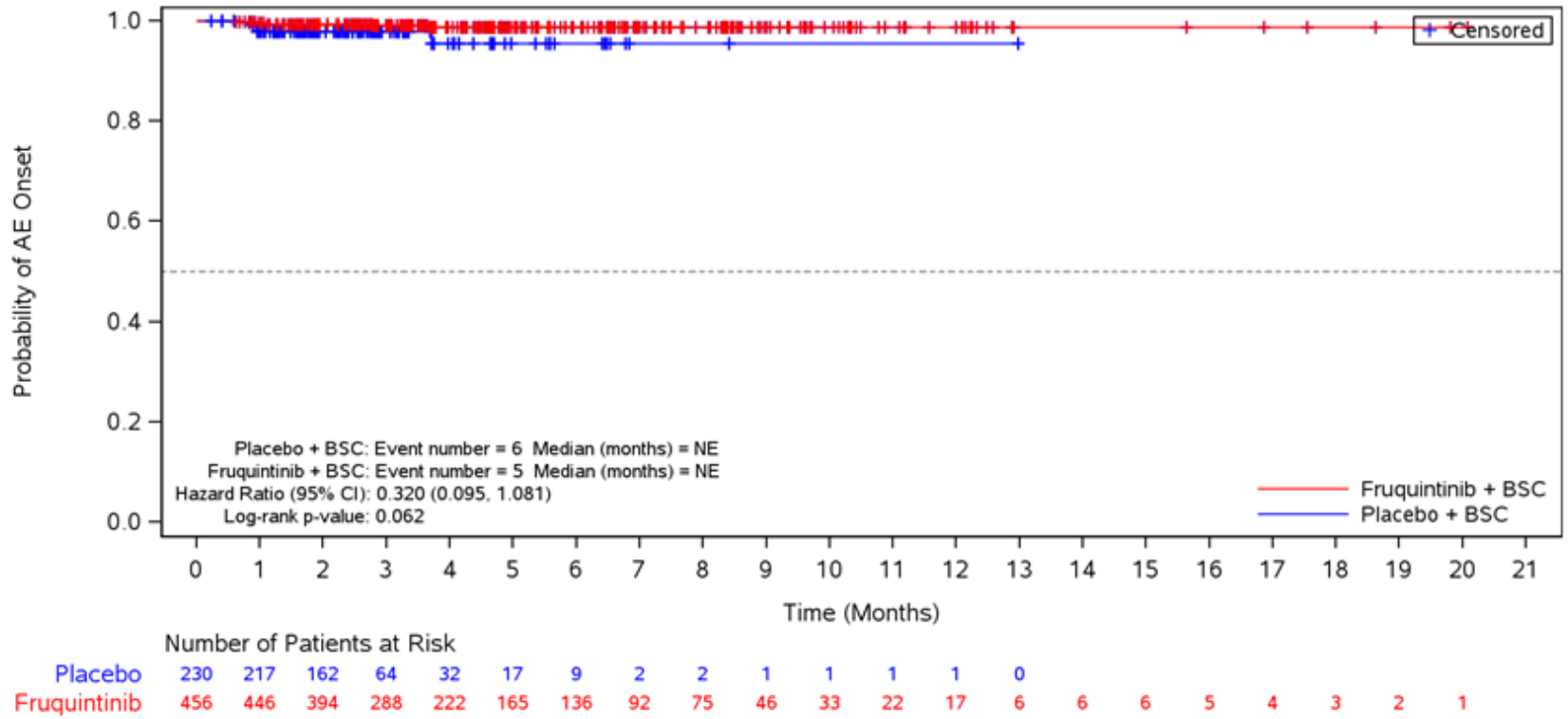
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE



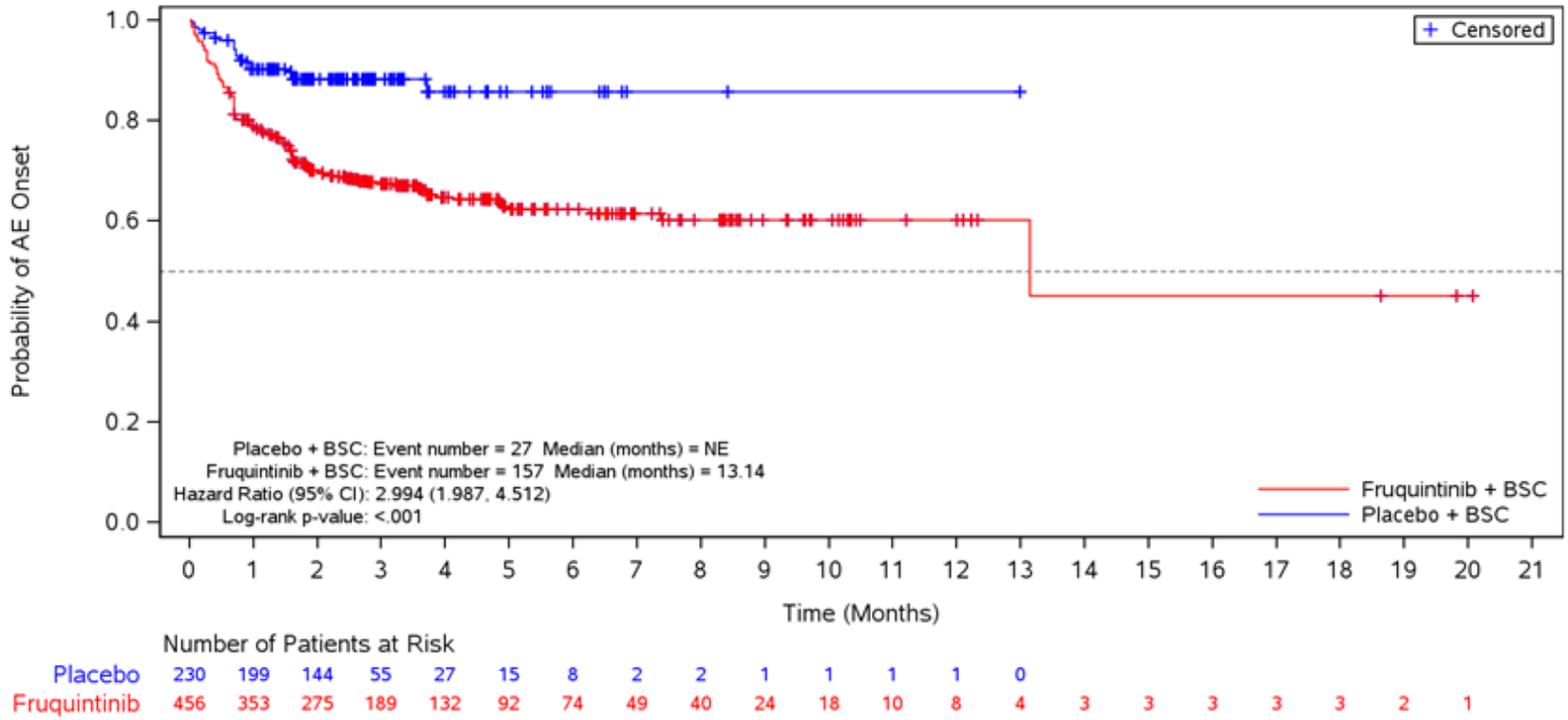
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE



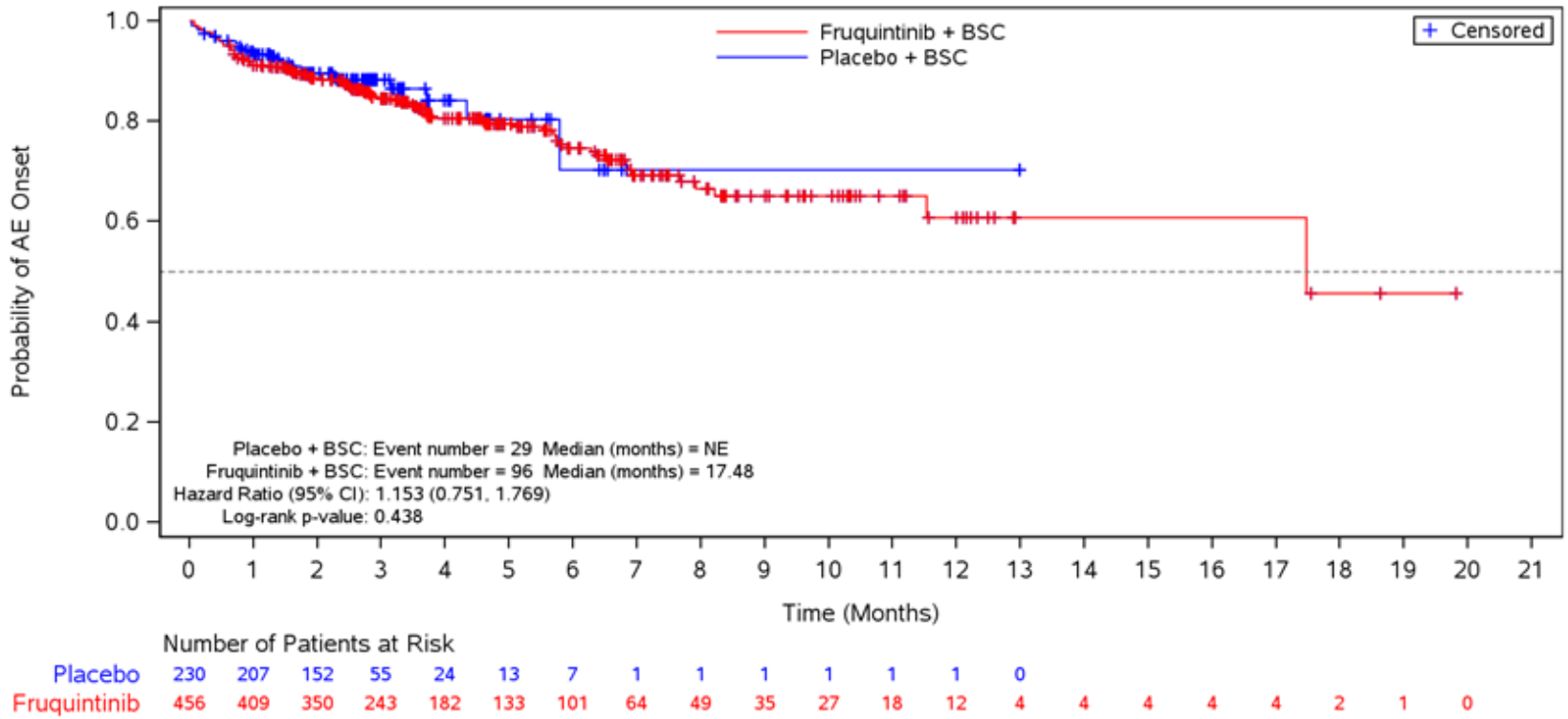
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE



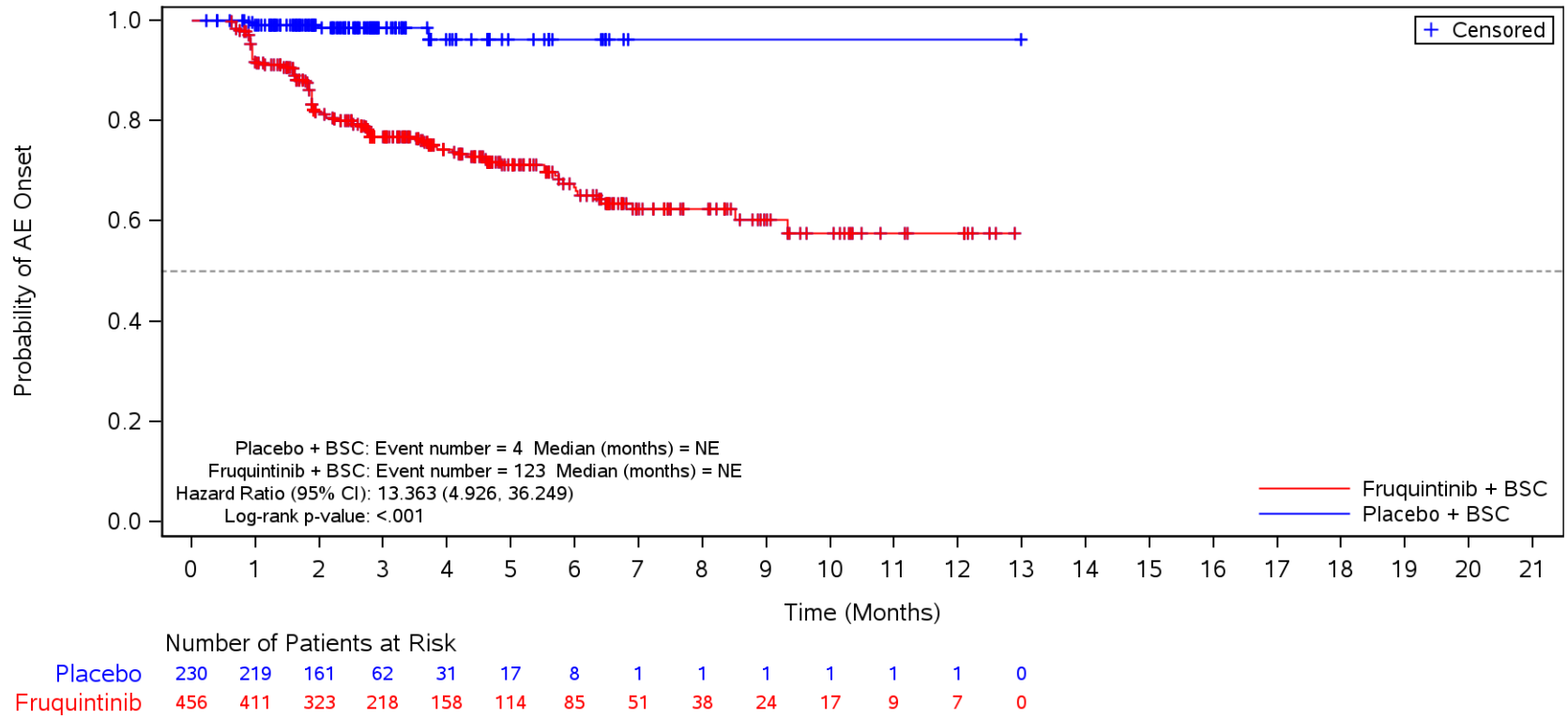
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Infections
Safety Population
TEAE



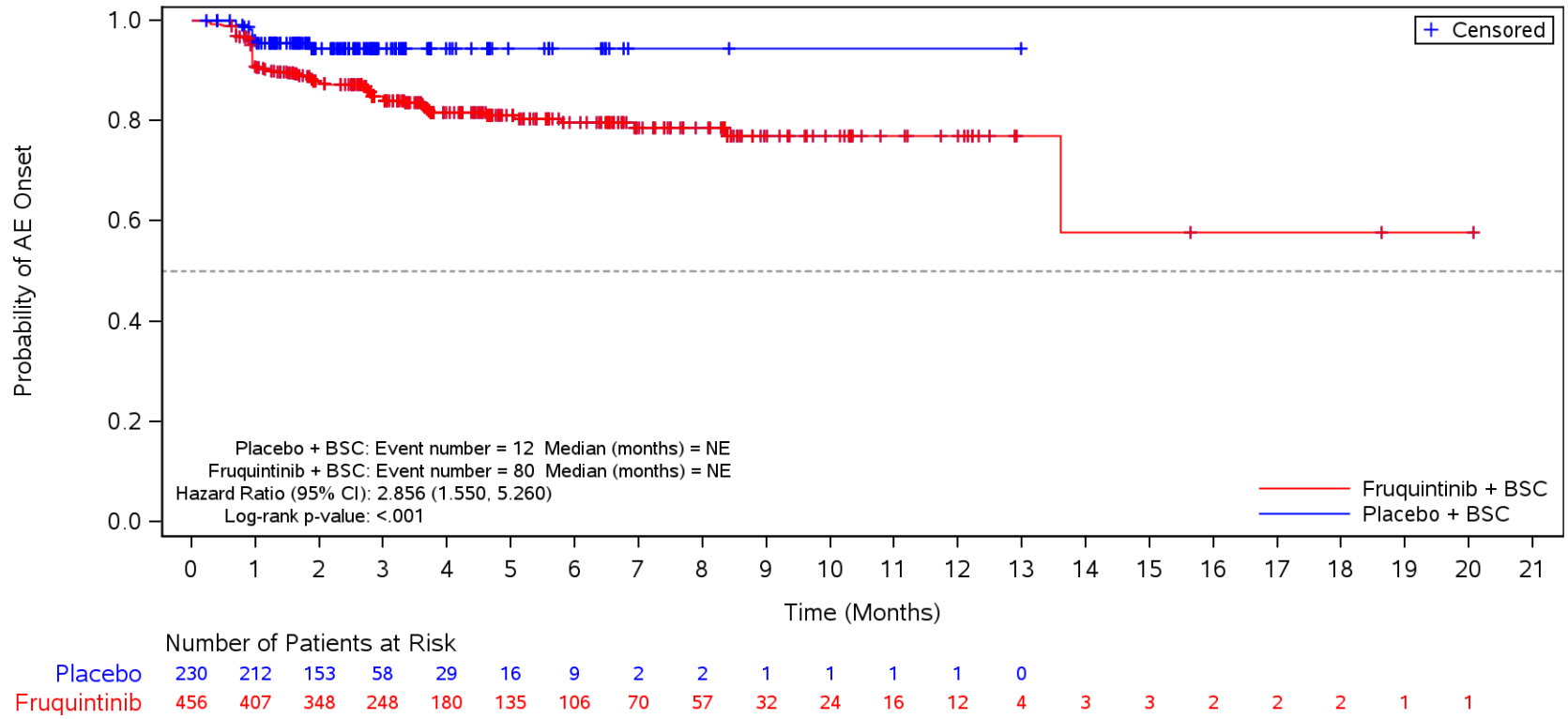
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE



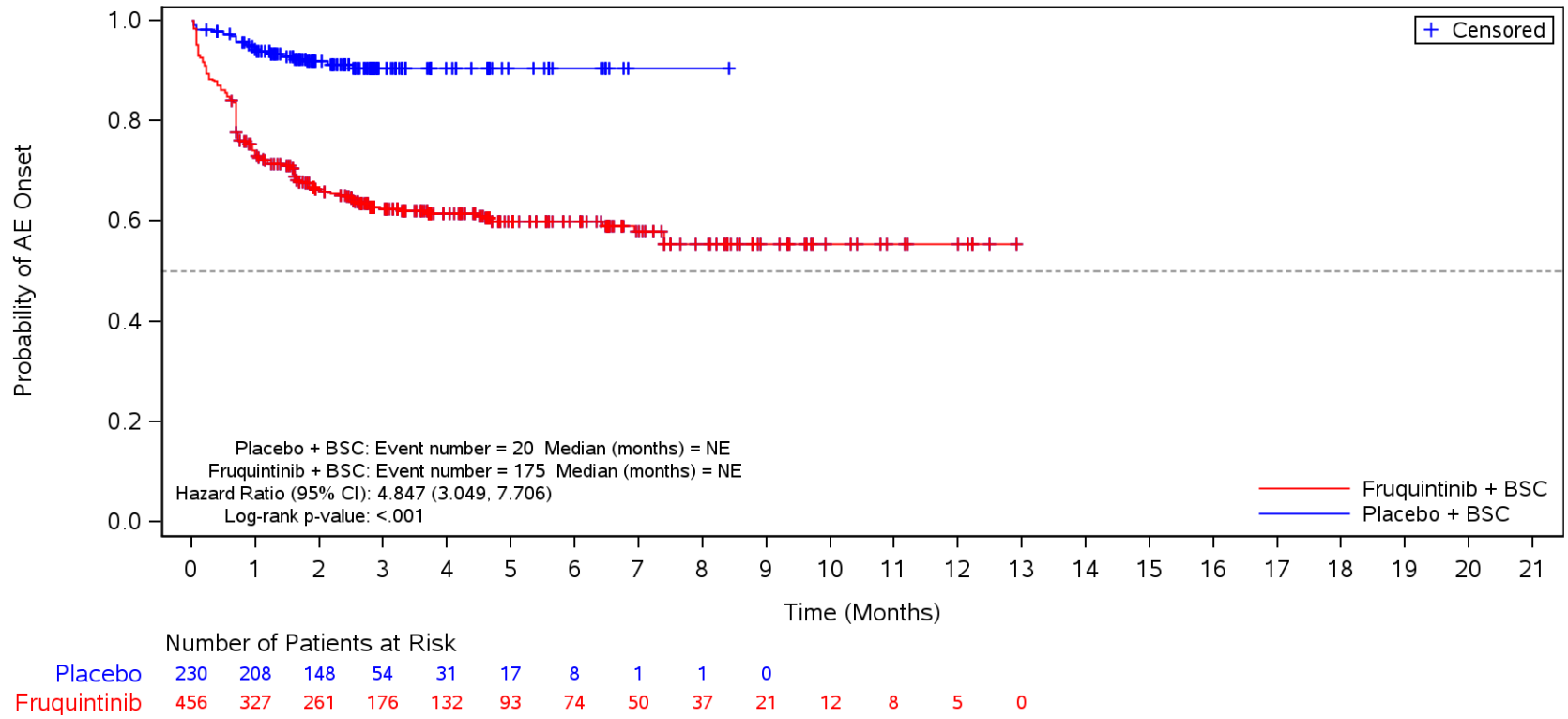
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE



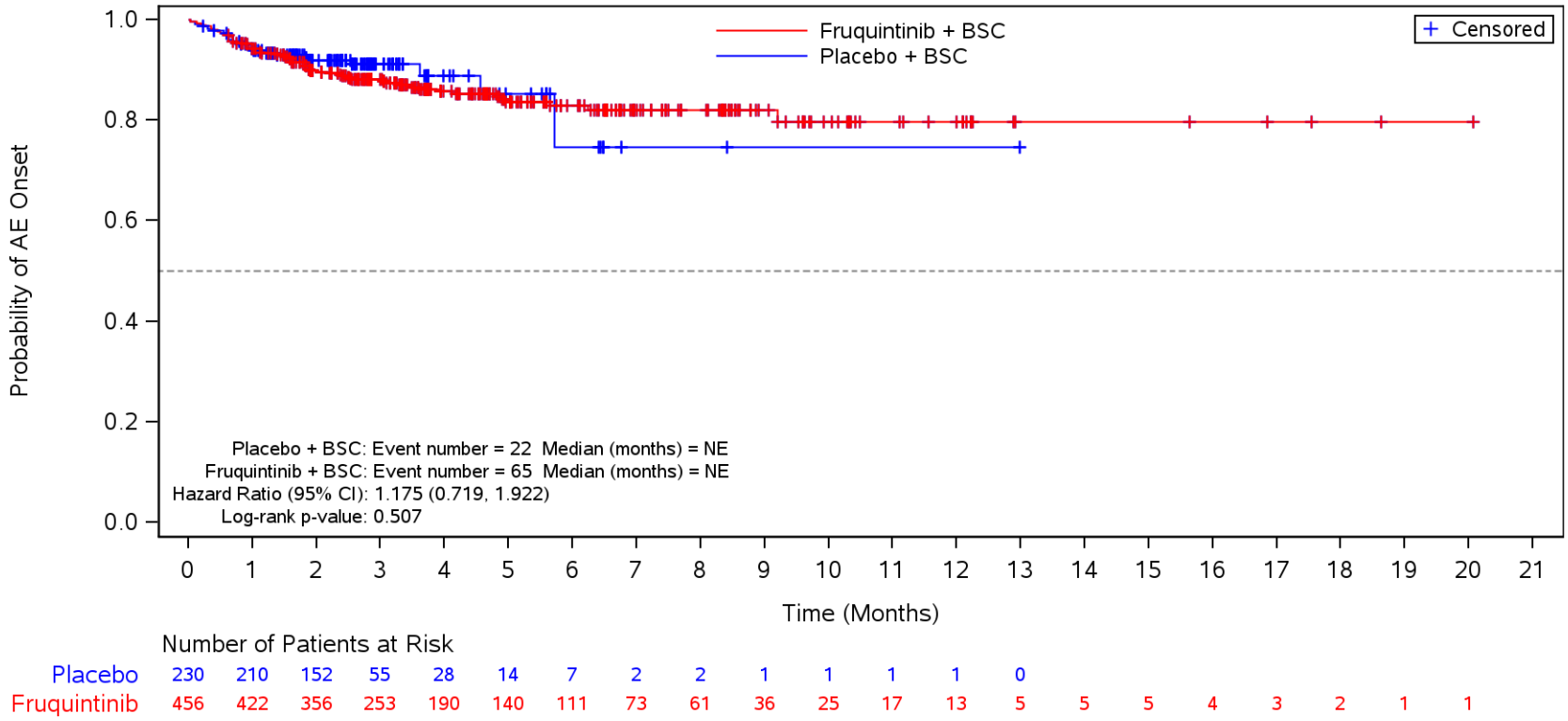
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE



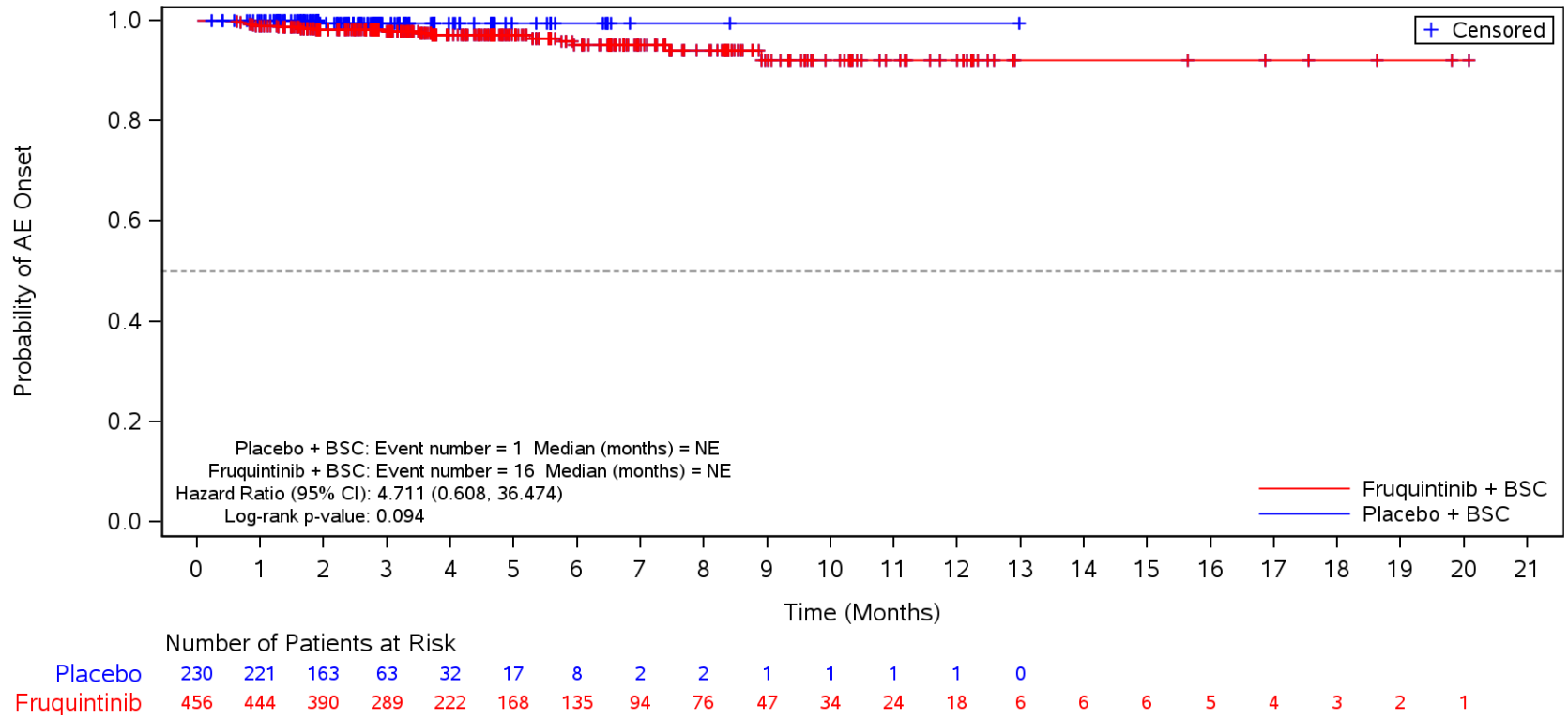
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE



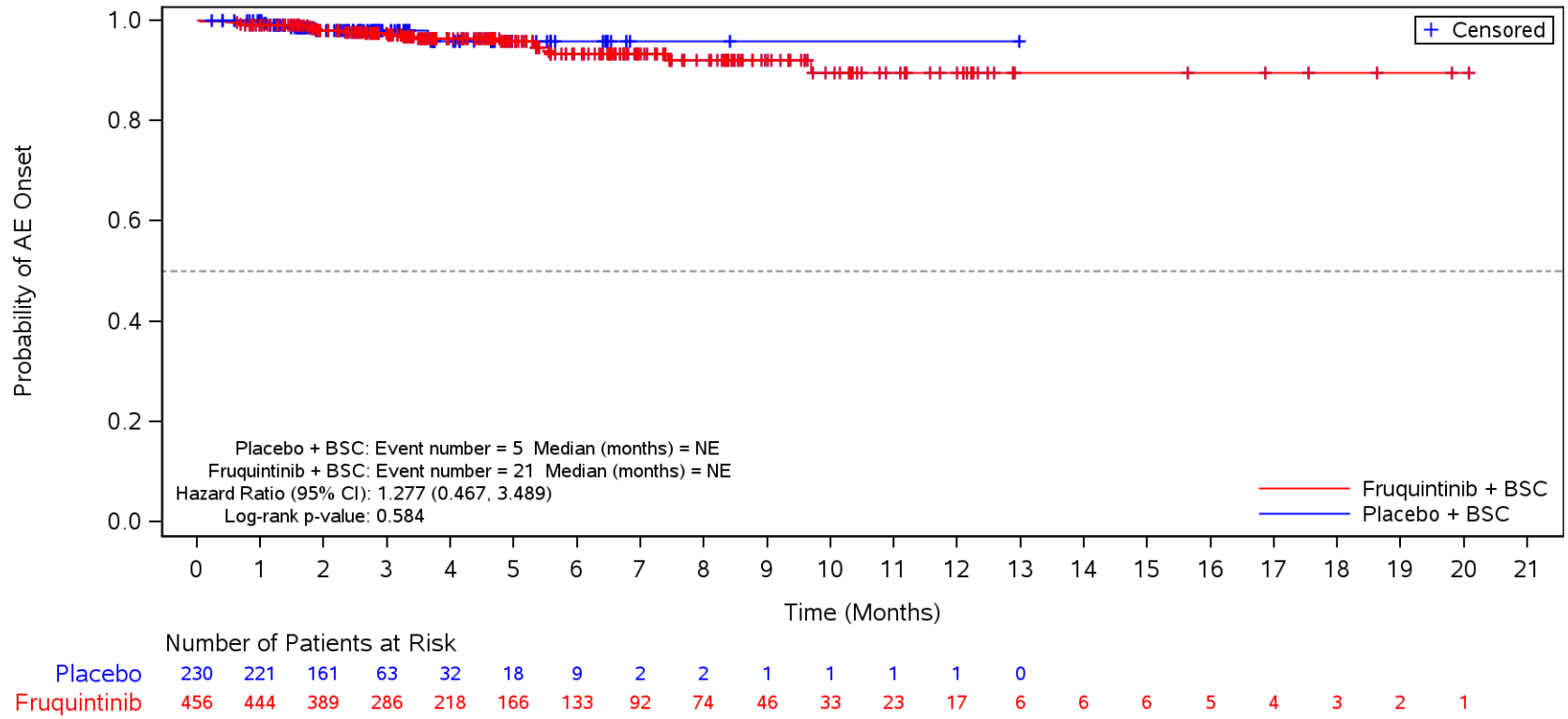
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE



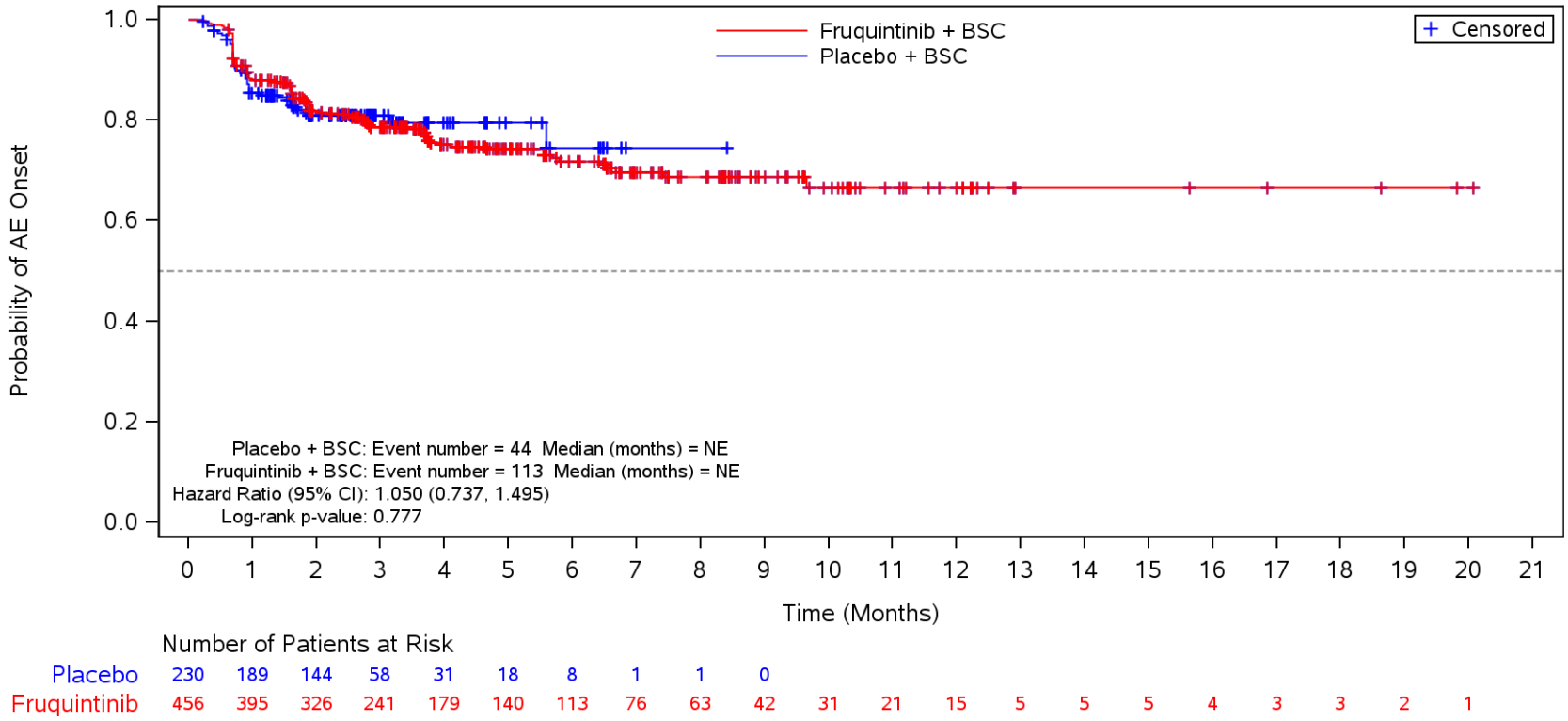
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE



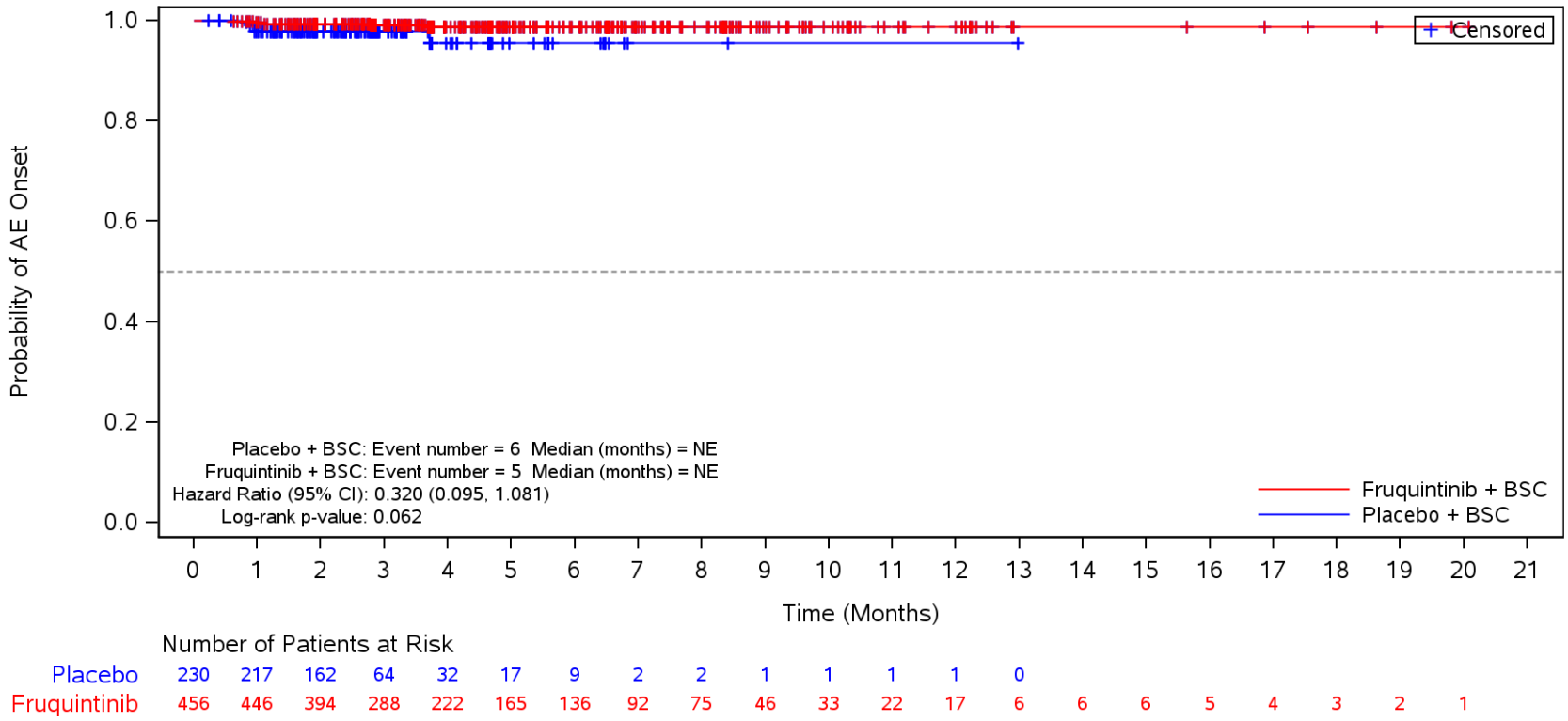
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE



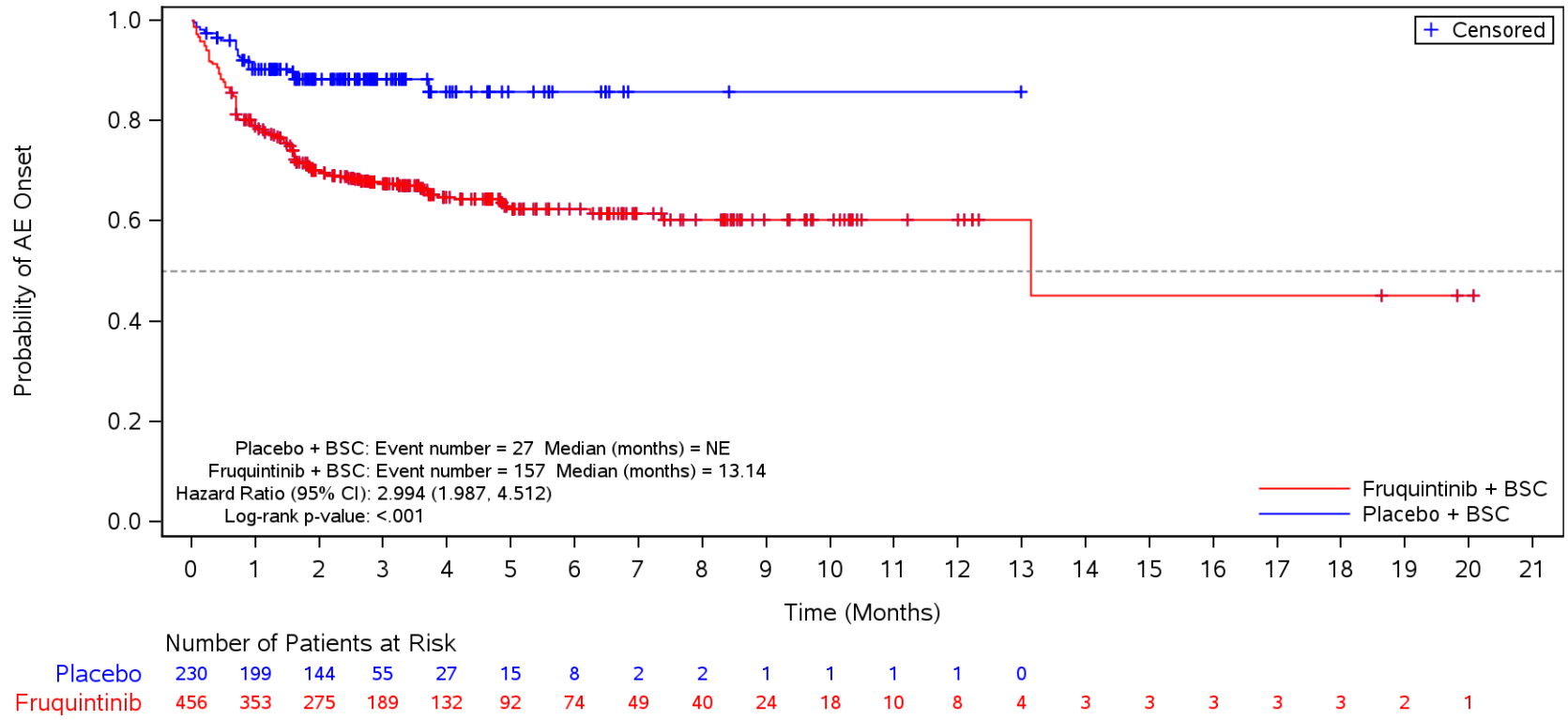
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE

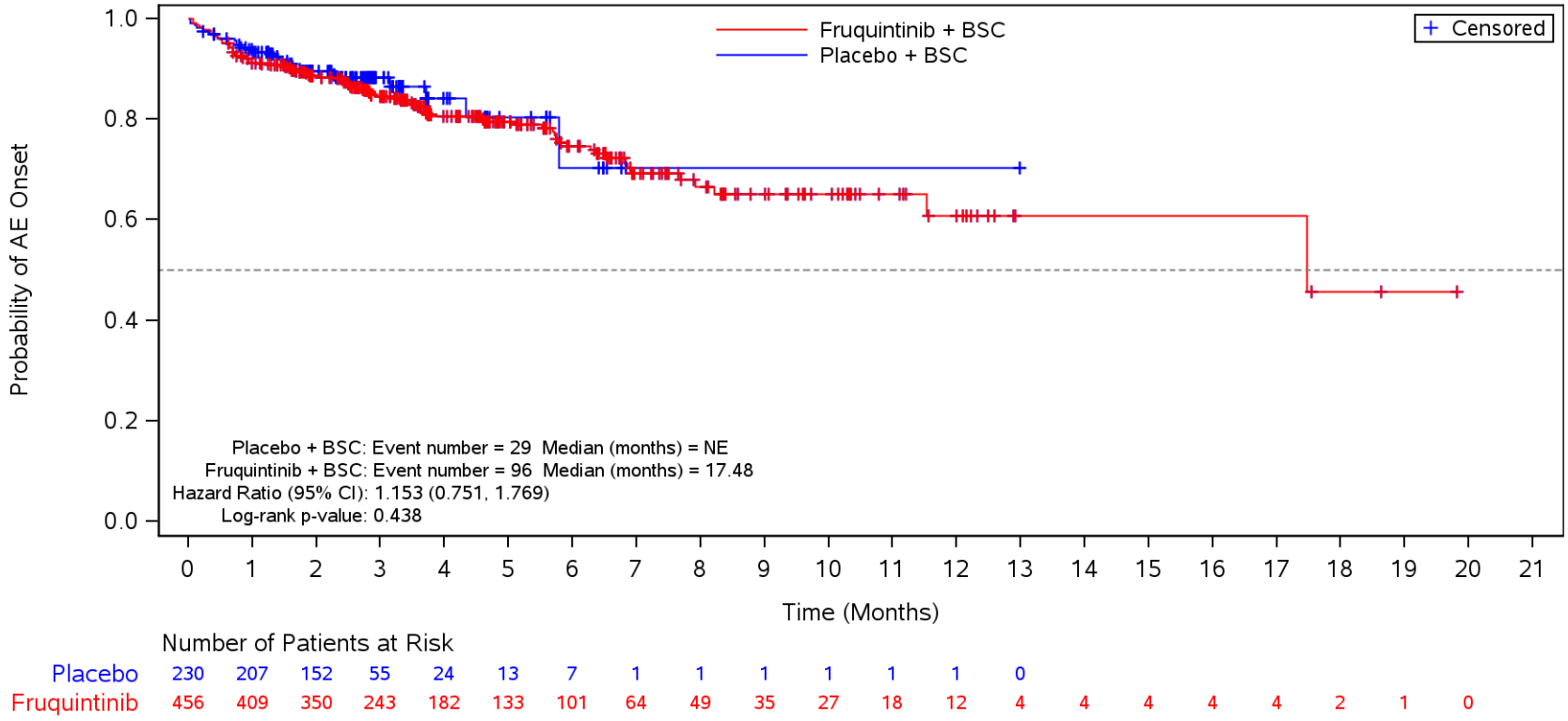


BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.1.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.


Fruquintinib + BSC
Placebo + BSC
Censored
Probability of AE Onset
1.0
0.8
0.6
0.4
0.2
0.0
Placebo + BSC: Event number = 29 Median (months) = NE
Fruquintinib + BSC: Event number = 96 Median (months) = 17.48
Hazard Ratio (95% CI): 1.153 (0.751, 1.769)
Log-rank p-value: 0.438
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Time (Months)
Number of Patients at Risk
Placebo 230 207 152 55 24 13 7 1 1 1 1 1 1 0
Fruquintinib 456 409 350 243 182 133 101 64 49 35 27 18 12 4 4 4 4 4 2 1 0

2.1.7 AESI des NCI CTCAE-Grads ≤ 2

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	121 (26.5)
Number of Subjects Censored, n (%)	226 (98.3)	335 (73.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	3.84 (2.73, 5.68)
Median (95% CI)	NE (NE, NE)	NE (9.33, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		13.225 (0.509)
95% CI		(4.874, 35.884)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.5 (96.8, 100.0)	77.1 (73.1, 81.2)
6 months	96.2 (91.5, 100.0)	67.4 (61.7, 73.1)
9 months	96.2 (91.5, 100.0)	60.9 (53.4, 68.4)
12 months	96.2 (91.5, 100.0)	58.1 (49.2, 67.0)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.83	2.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	77 (16.9)
Number of Subjects Censored, n (%)	219 (95.2)	379 (83.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.60 (6.93, NE)
Median (95% CI)	NE (NE, NE)	NE (13.60, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.60, NE)
Min, Max	0.2*, 13.0*	0.2, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.961 (0.324)
95% CI		(1.568, 5.592)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.0 (92.1, 97.9)	84.9 (81.5, 88.4)
6 months	95.0 (92.1, 97.9)	80.3 (76.0, 84.7)
9 months	95.0 (92.1, 97.9)	77.6 (72.0, 83.3)
12 months	95.0 (92.1, 97.9)	77.6 (72.0, 83.3)
18 months	NE (NE, NE)	58.2 (25.0, 91.4)
Median Follow-up Time (months)	2.79	3.33

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	18 (7.8)	144 (31.6)
Number of Subjects Censored, n (%)	212 (92.2)	312 (68.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	1.74 (1.05, 2.53)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 8.4*	0.0, 12.9*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		4.105 (0.251)
95% CI		(2.512, 6.710)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	91.4 (87.6, 95.3)	69.1 (64.7, 73.5)
6 months	91.4 (87.6, 95.3)	67.3 (62.7, 71.9)
9 months	NE (NE, NE)	61.8 (55.5, 68.1)
12 months	NE (NE, NE)	61.8 (55.5, 68.1)
18 months	NE (NE, NE)	NE (NE, NE)
Median Follow-up Time (months)	2.79	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	18 (7.8)	60 (13.2)
Number of Subjects Censored, n (%)	212 (92.2)	396 (86.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.72, NE)	NE (9.20, NE)
Median (95% CI)	NE (5.72, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.374 (0.273)
95% CI		(0.806, 2.345)
Log-rank p-value		0.206

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	92.0 (88.3, 95.7)	88.8 (85.9, 91.8)
6 months	80.5 (59.2, 100.0)	84.5 (80.5, 88.5)
9 months	80.5 (59.2, 100.0)	83.7 (79.5, 88.0)
12 months	80.5 (59.2, 100.0)	81.4 (75.3, 87.5)
18 months	NE (NE, NE)	81.4 (75.3, 87.5)
Median Follow-up Time (months)	2.79	3.48

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	6 (1.3)
Number of Subjects Censored, n (%)	229 (99.6)	450 (98.7)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.936 (1.101)
95% CI		(0.224, 16.737)
Log-rank p-value		0.532

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.4 (98.2, 100.0)	99.0 (98.0, 100.0)
6 months	99.4 (98.2, 100.0)	97.9 (96.1, 99.7)
9 months	99.4 (98.2, 100.0)	97.9 (96.1, 99.7)
12 months	99.4 (98.2, 100.0)	97.9 (96.1, 99.7)
18 months	NE (NE, NE)	97.9 (96.1, 99.7)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	3 (1.3)	8 (1.8)
Number of Subjects Censored, n (%)	227 (98.7)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.860 (0.702)
95% CI		(0.217, 3.401)
Log-rank p-value		0.894

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.5 (96.9, 100.0)	98.8 (97.7, 99.8)
6 months	98.5 (96.9, 100.0)	97.5 (95.4, 99.6)
9 months	98.5 (96.9, 100.0)	96.3 (93.2, 99.4)
12 months	98.5 (96.9, 100.0)	96.3 (93.2, 99.4)
18 months	NE (NE, NE)	96.3 (93.2, 99.4)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	39 (17.0)	104 (22.8)
Number of Subjects Censored, n (%)	191 (83.0)	352 (77.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (5.59, NE)	5.68 (3.68, 9.89)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 8.4*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.083 (0.191)
95% CI		(0.745, 1.573)
Log-rank p-value		0.670

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	83.1 (78.1, 88.1)	80.4 (76.6, 84.1)
6 months	76.5 (65.5, 87.6)	74.0 (69.2, 78.8)
9 months	NE (NE, NE)	70.7 (65.2, 76.3)
12 months	NE (NE, NE)	68.6 (61.8, 75.4)
18 months	NE (NE, NE)	68.6 (61.8, 75.4)
Median Follow-up Time (months)	2.79	3.32

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	2 (0.4)
Number of Subjects Censored, n (%)	226 (98.3)	454 (99.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.136 (0.927)
95% CI		(0.022, 0.833)
Log-rank p-value		0.023

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.7 (97.1, 100.0)	99.8 (99.3, 100.0)
6 months	96.4 (91.8, 100.0)	99.3 (98.4, 100.0)
9 months	96.4 (91.8, 100.0)	99.3 (98.4, 100.0)
12 months	96.4 (91.8, 100.0)	99.3 (98.4, 100.0)
18 months	NE (NE, NE)	99.3 (98.4, 100.0)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	26 (11.3)	151 (33.1)
Number of Subjects Censored, n (%)	204 (88.7)	305 (66.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	1.61 (1.12, 2.04)
Median (95% CI)	NE (NE, NE)	13.60 (13.60, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.60, NE)
Min, Max	0.0, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.965 (0.213)
95% CI		(1.952, 4.503)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	88.7 (84.6, 92.9)	68.8 (64.4, 73.1)
6 months	86.3 (80.0, 92.5)	63.8 (58.7, 68.8)
9 months	86.3 (80.0, 92.5)	61.6 (55.9, 67.4)
12 months	86.3 (80.0, 92.5)	61.6 (55.9, 67.4)
18 months	NE (NE, NE)	46.2 (19.7, 72.7)
Median Follow-up Time (months)	2.78	2.83

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	21 (9.1)	80 (17.5)
Number of Subjects Censored, n (%)	209 (90.9)	376 (82.5)
Time to first TEAE (months)		
25% percentile (95% CI)	5.78 (4.34, NE)	6.87 (5.72, 11.53)
Median (95% CI)	NE (5.78, NE)	17.48 (17.48, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (17.48, NE)
Min, Max	0.0, 13.0*	0.1, 19.8*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.253 (0.254)
95% CI		(0.762, 2.061)
Log-rank p-value		0.296

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.5.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE ≤ CTCAE Grade 2

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	91.4 (87.5, 95.2)	88.7 (85.7, 91.7)
6 months	74.4 (53.3, 95.6)	79.6 (74.6, 84.5)
9 months	74.4 (53.3, 95.6)	68.0 (60.2, 75.8)
12 months	74.4 (53.3, 95.6)	63.8 (52.9, 74.6)
18 months	NE (NE, NE)	47.8 (19.6, 76.1)
Median Follow-up Time (months)	2.79	3.40

* indicates censored value.

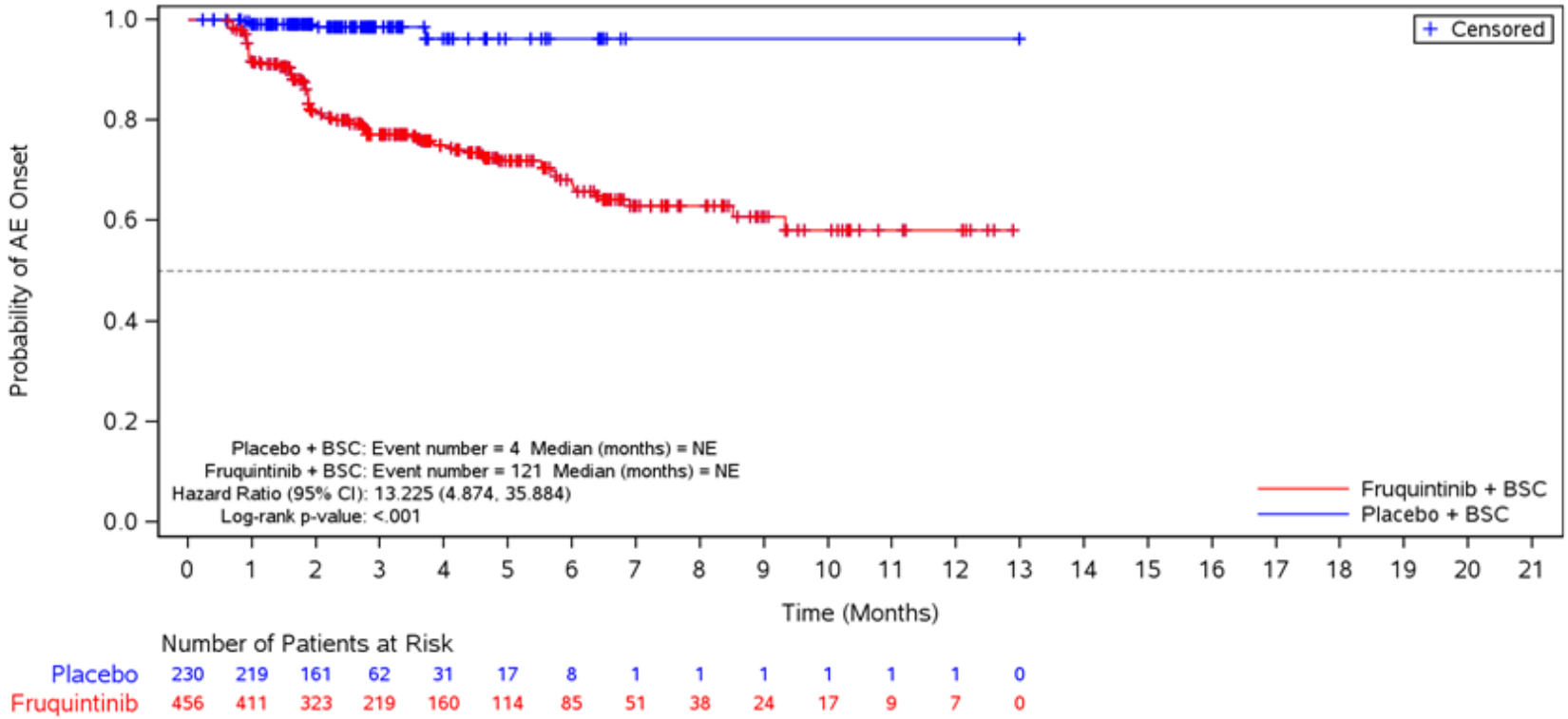
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

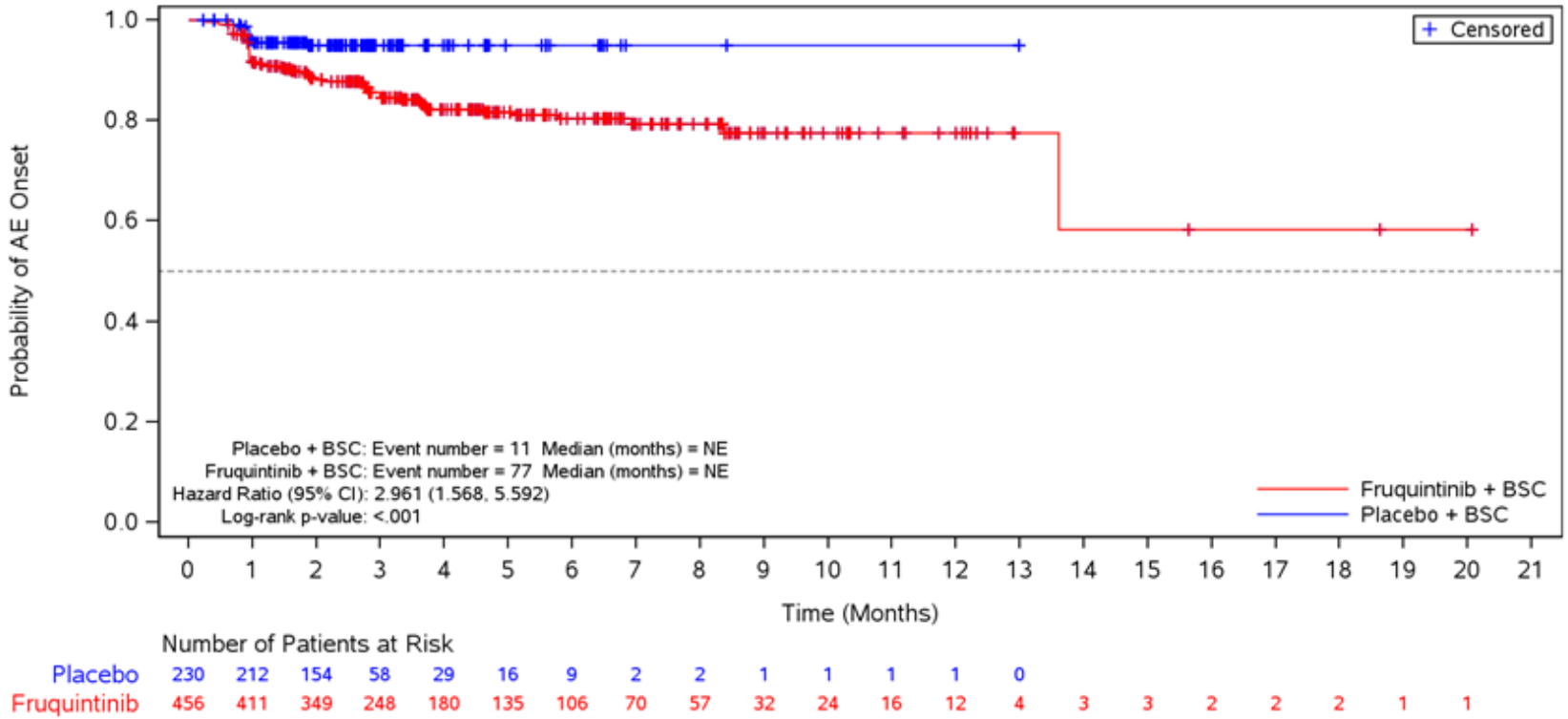
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≤ CTCAE Grade 2



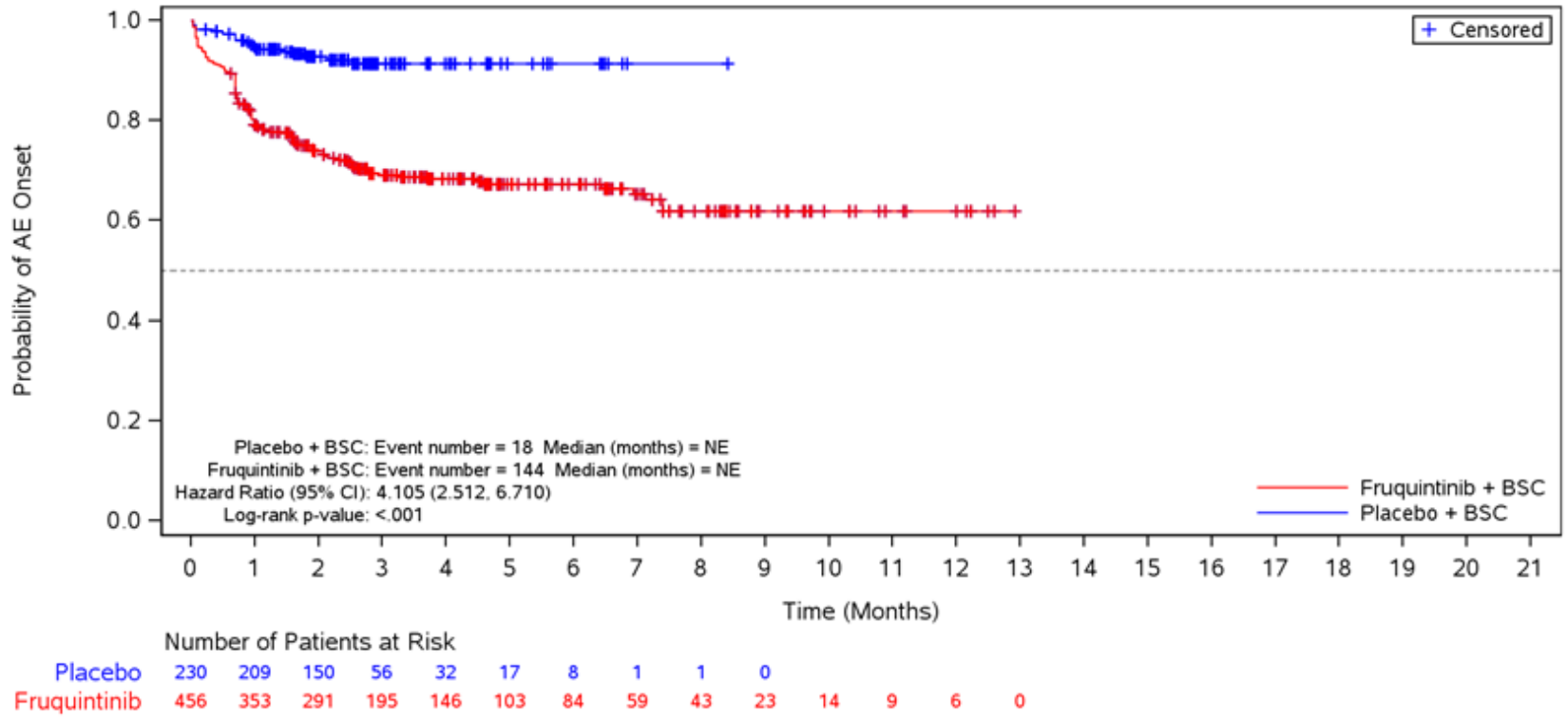
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≤ CTCAE Grade 2



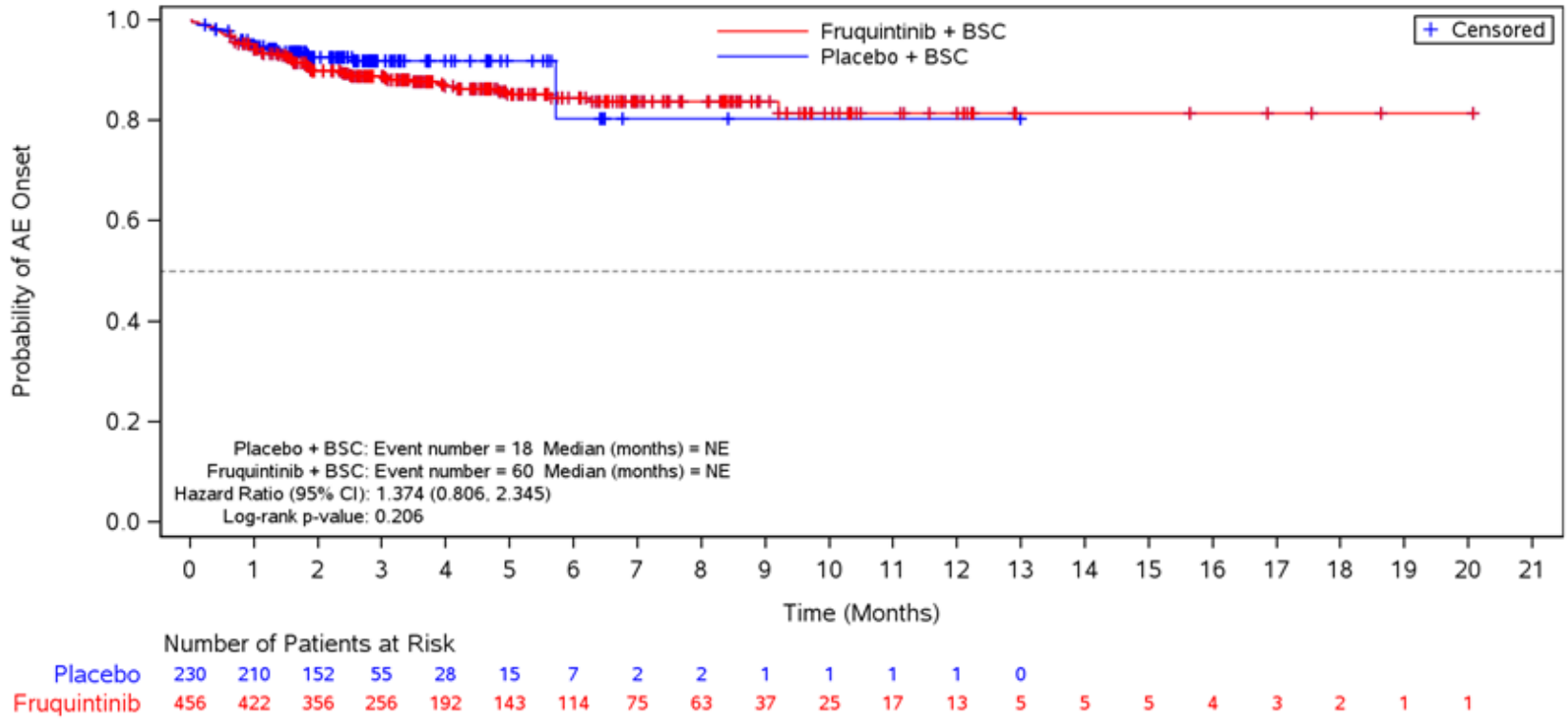
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≤ CTCAE Grade 2



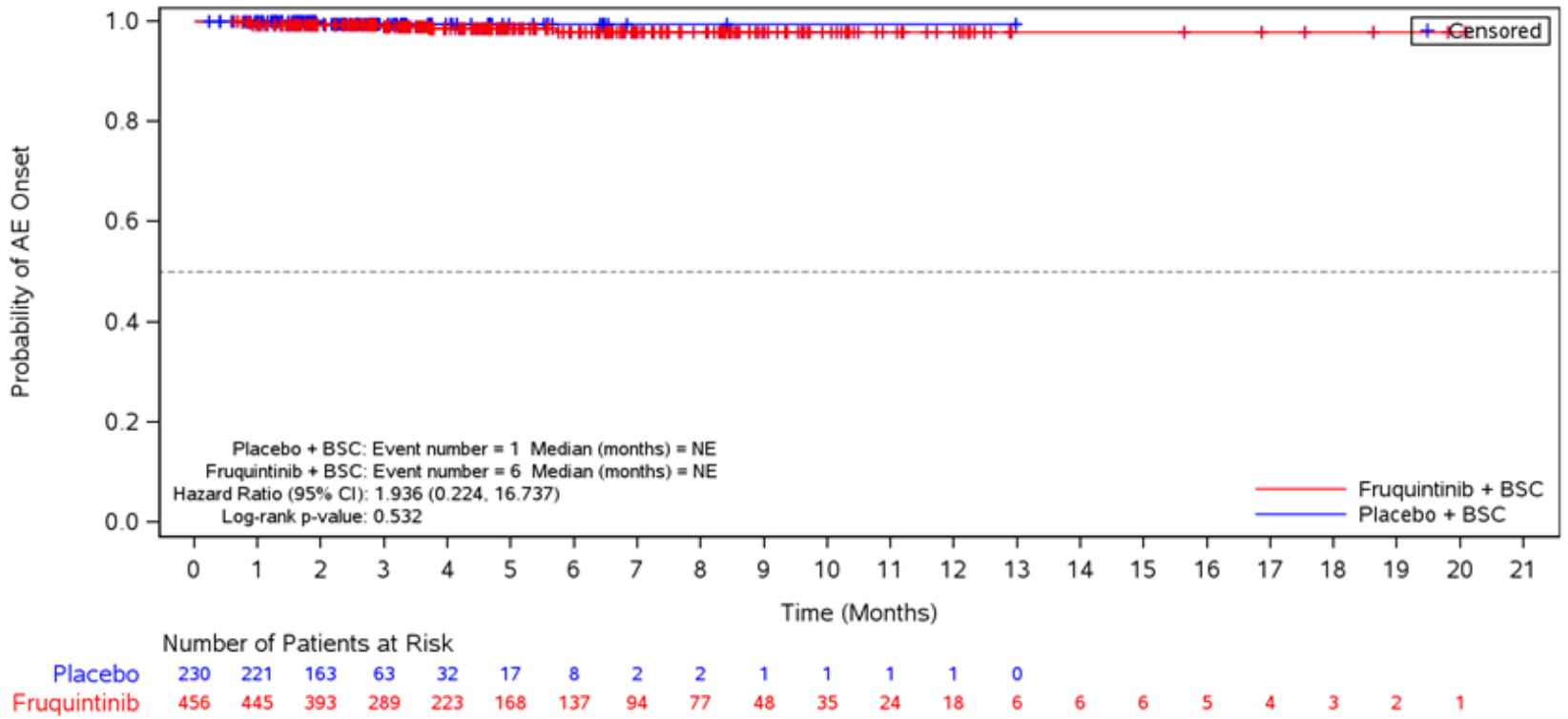
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≤ CTCAE Grade 2



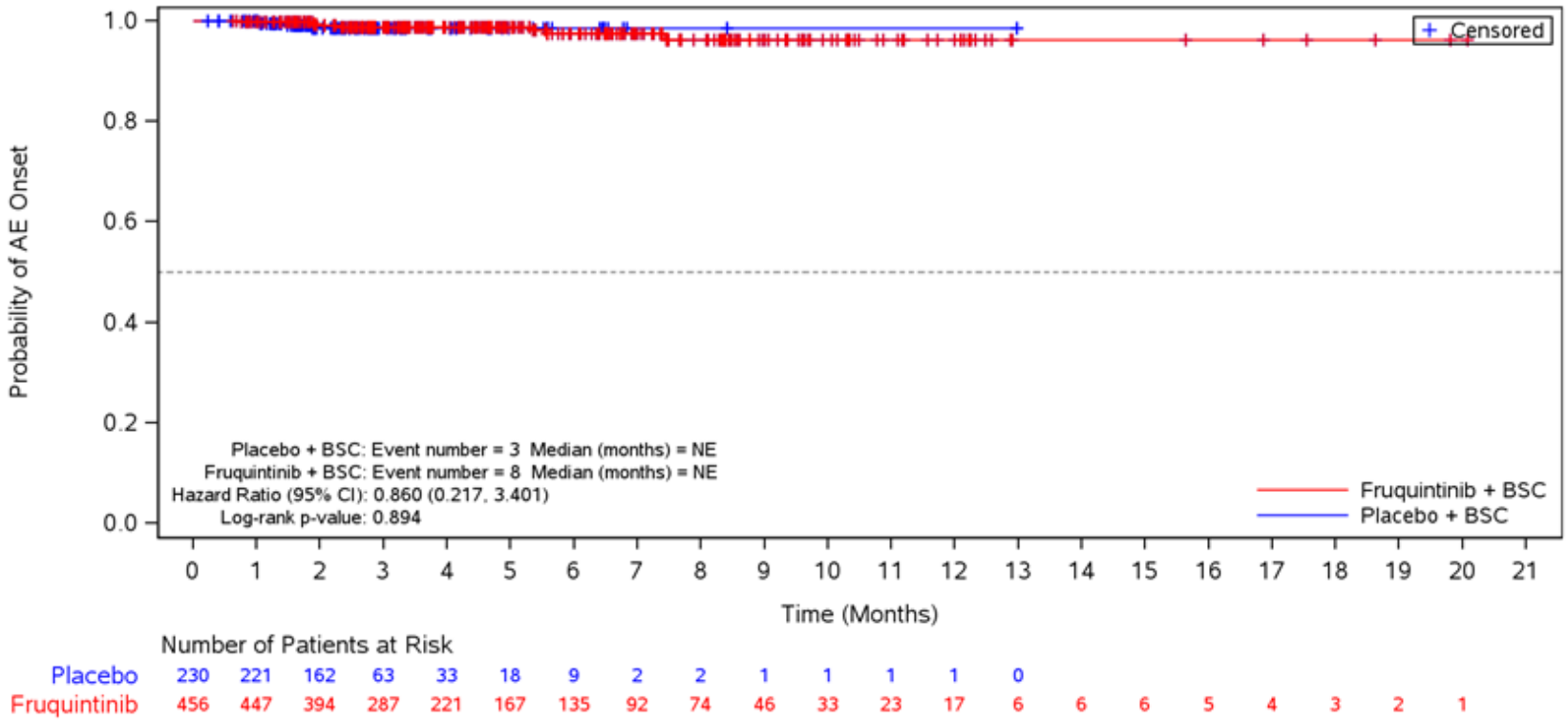
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≤ CTCAE Grade 2



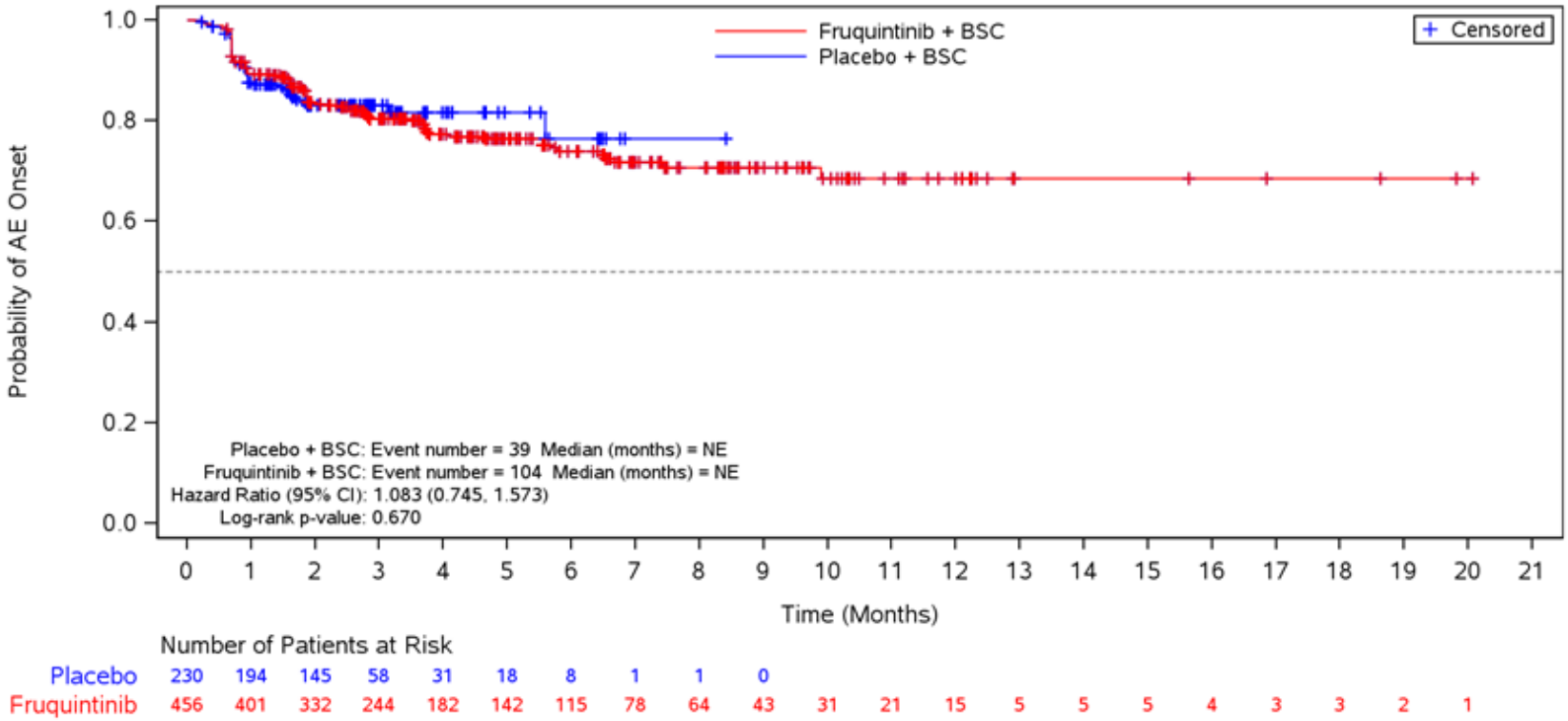
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≤ CTCAE Grade 2



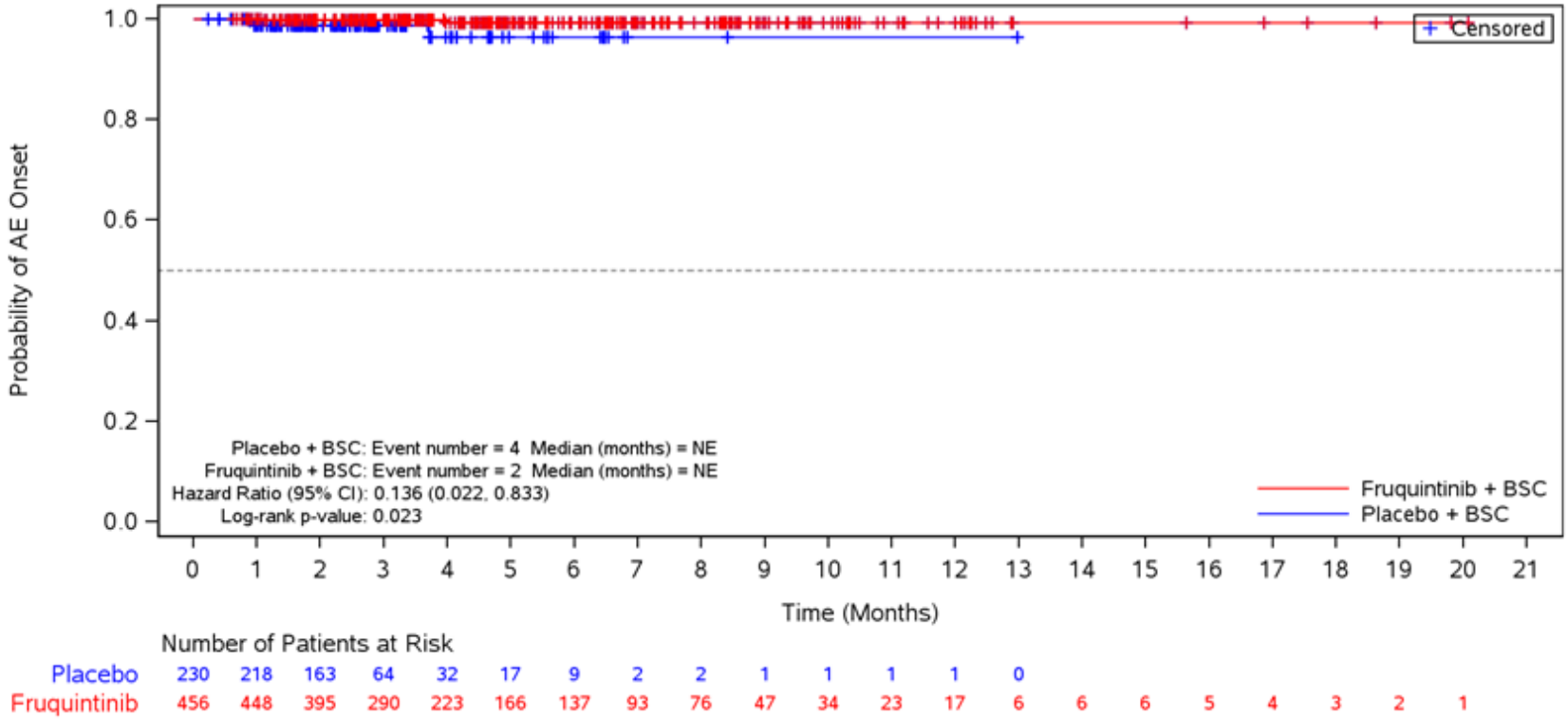
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≤ CTCAE Grade 2



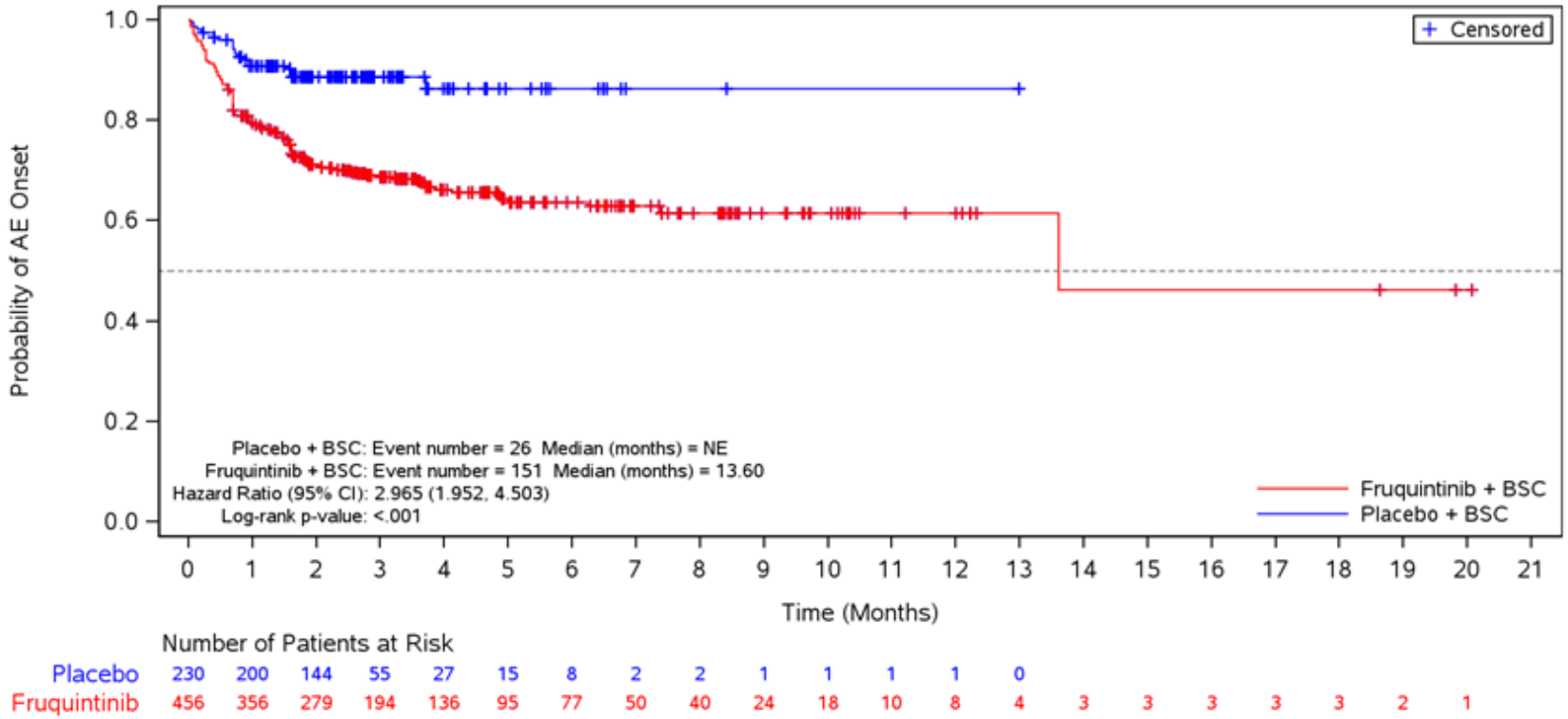
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≤ CTCAE Grade 2



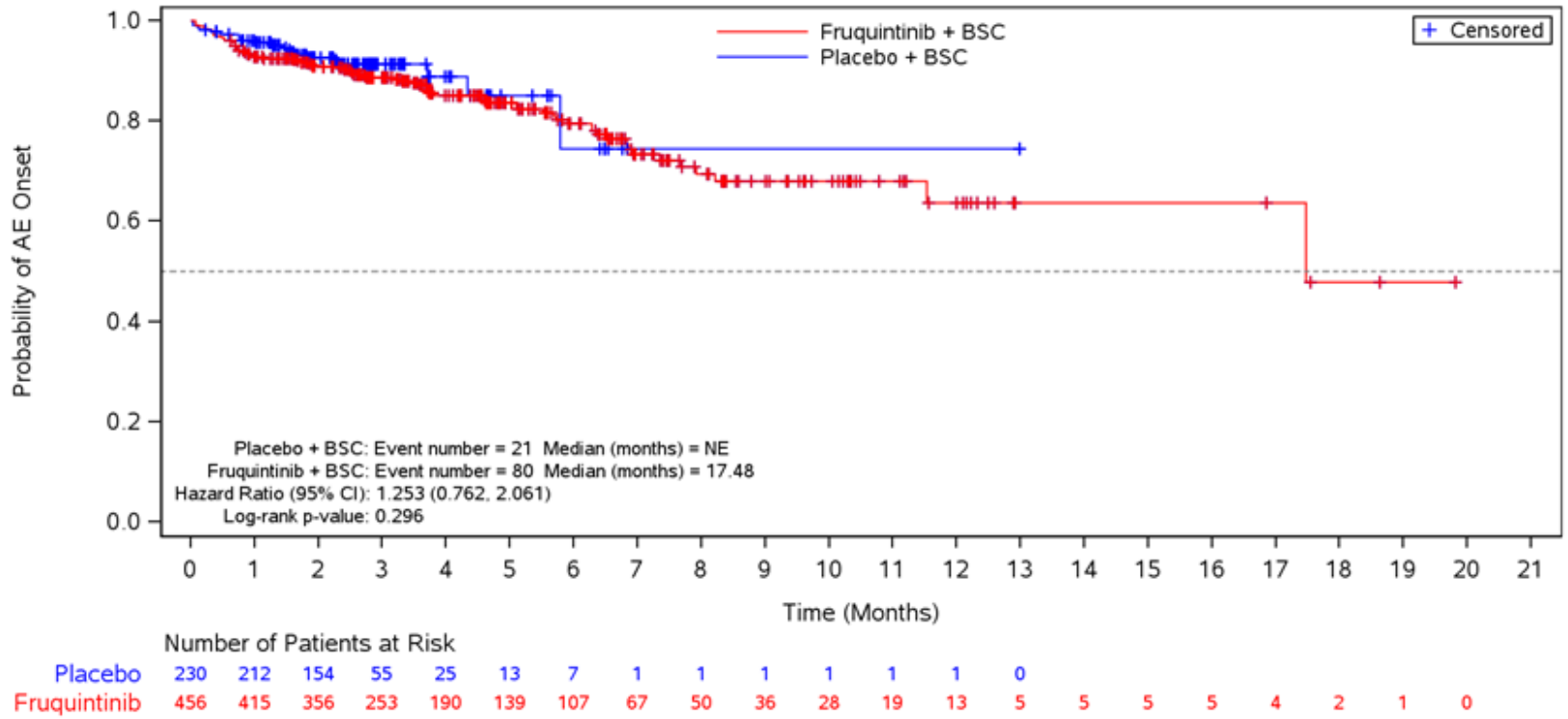
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≤ CTCAE Grade 2



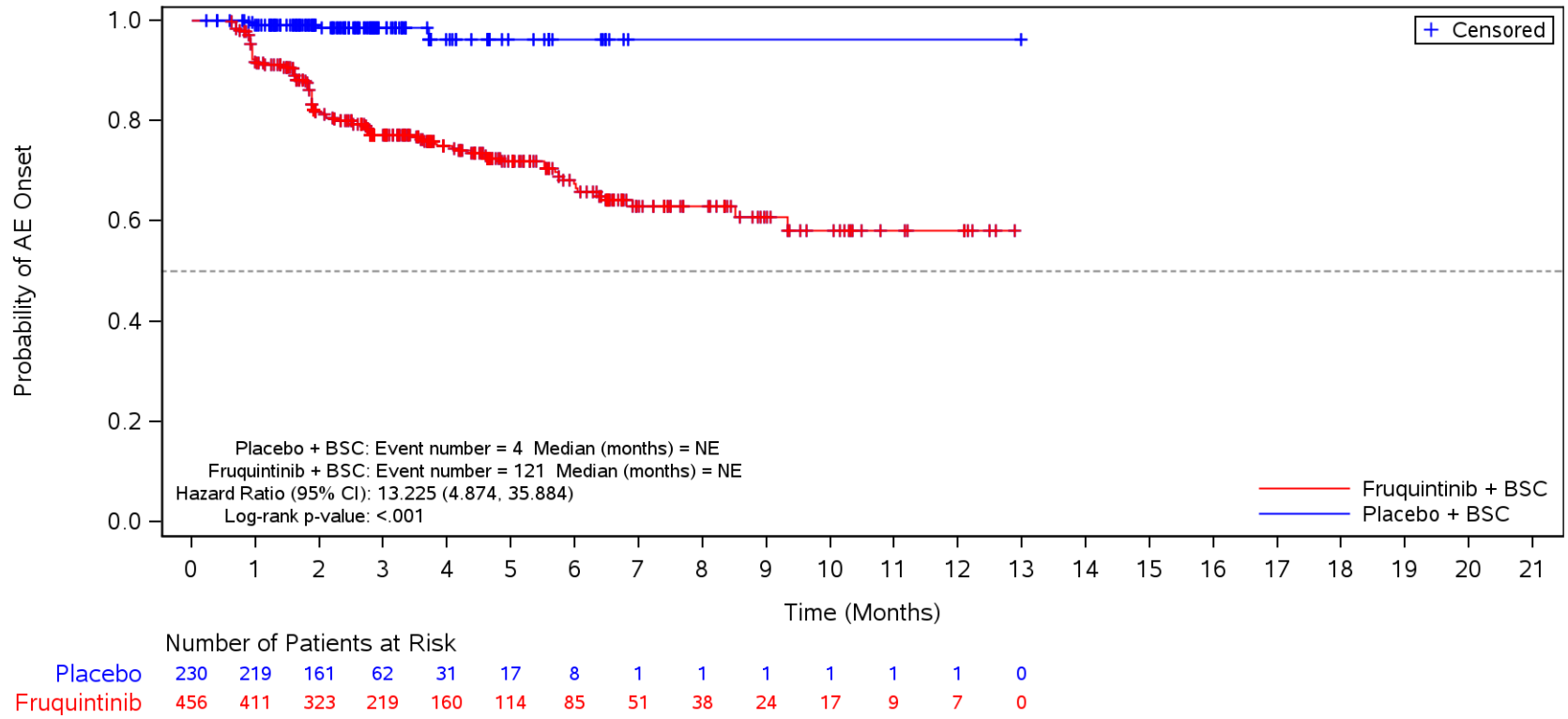
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Infections
Safety Population
TEAE ≤ CTCAE Grade 2



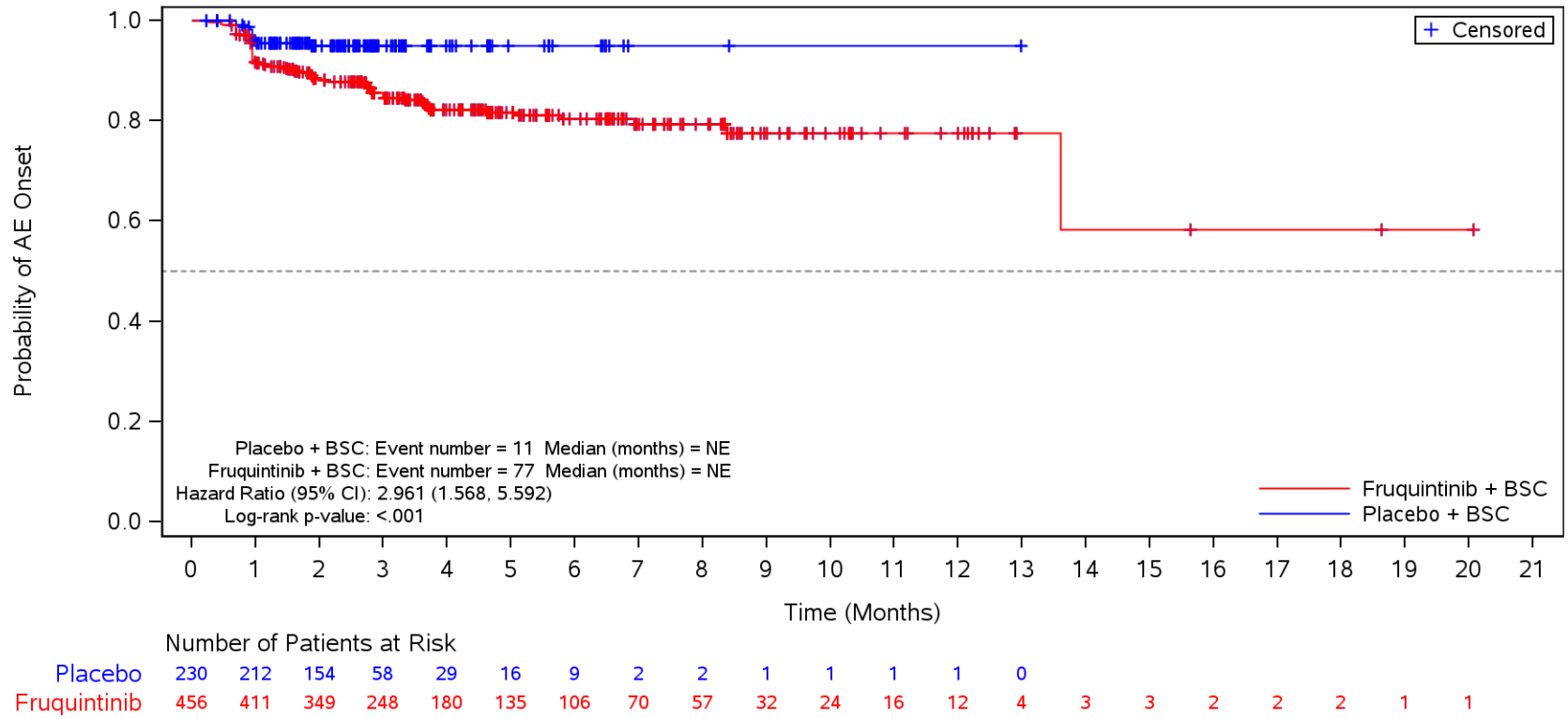
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≤ CTCAE Grade 2



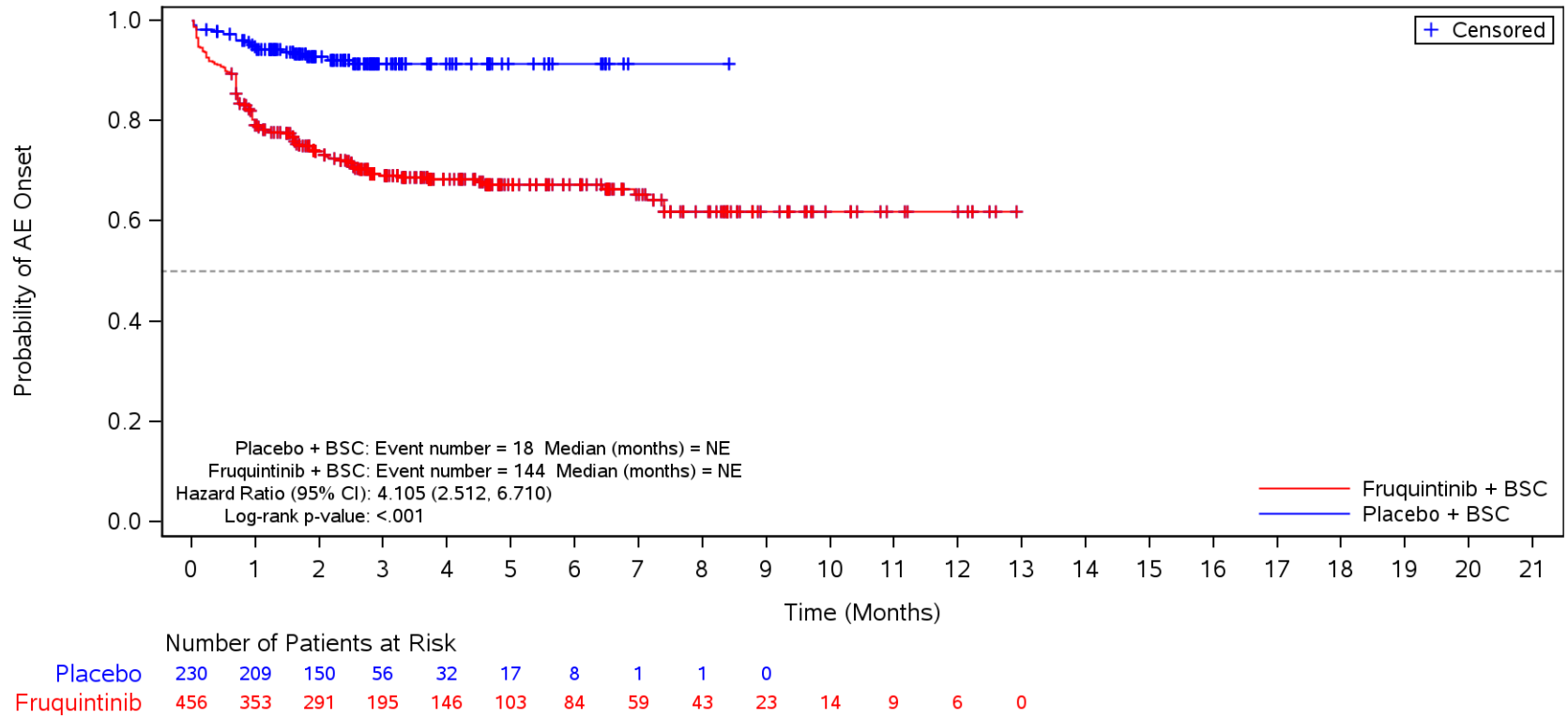
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≤ CTCAE Grade 2



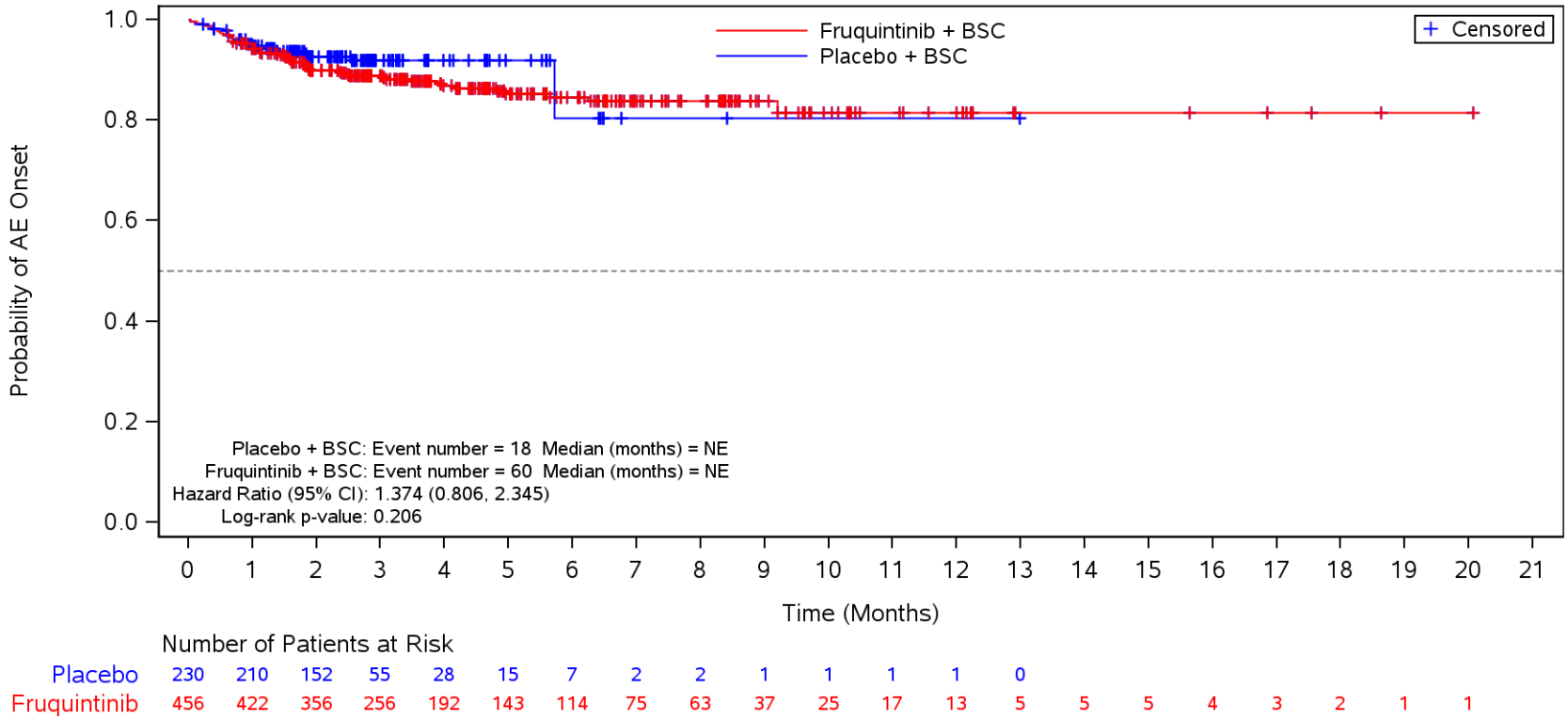
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≤ CTCAE Grade 2



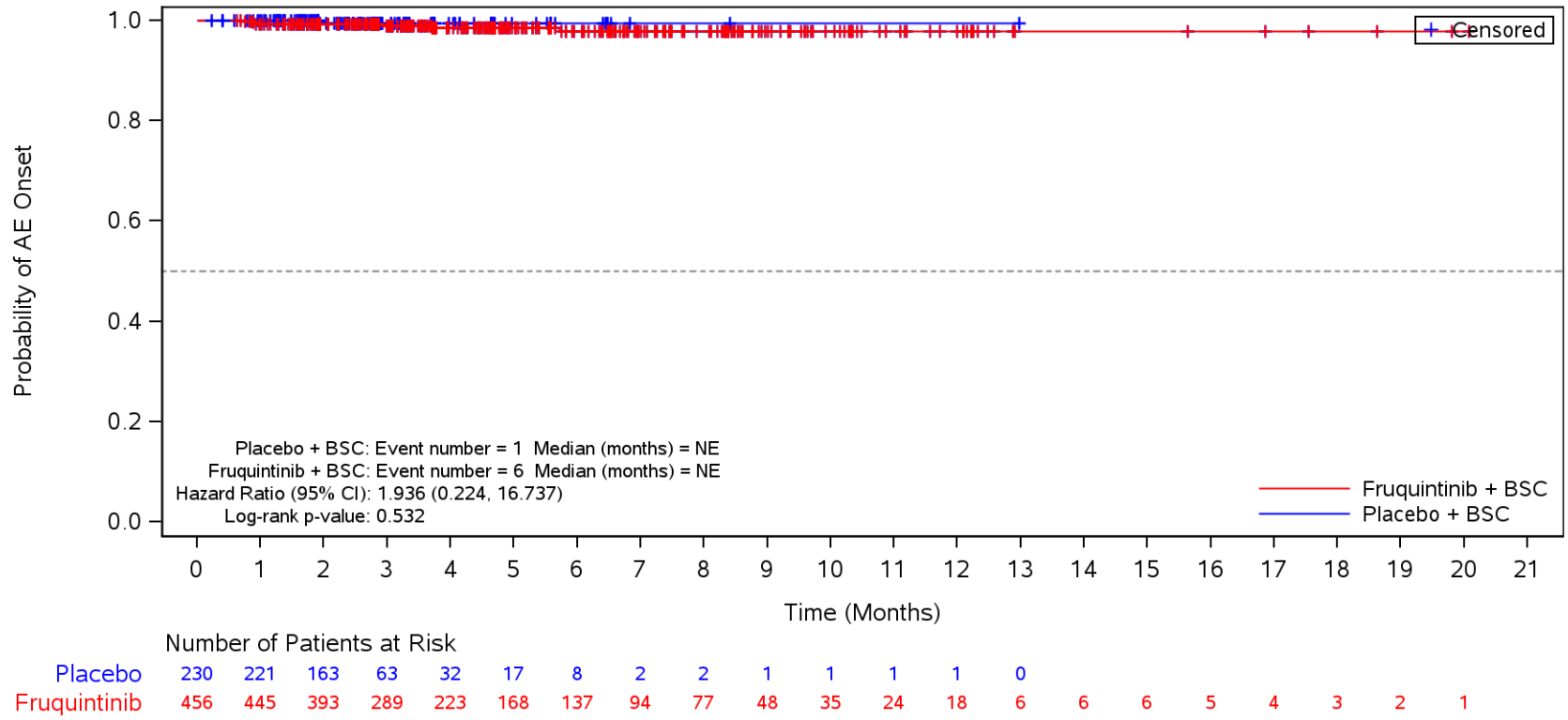
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≤ CTCAE Grade 2



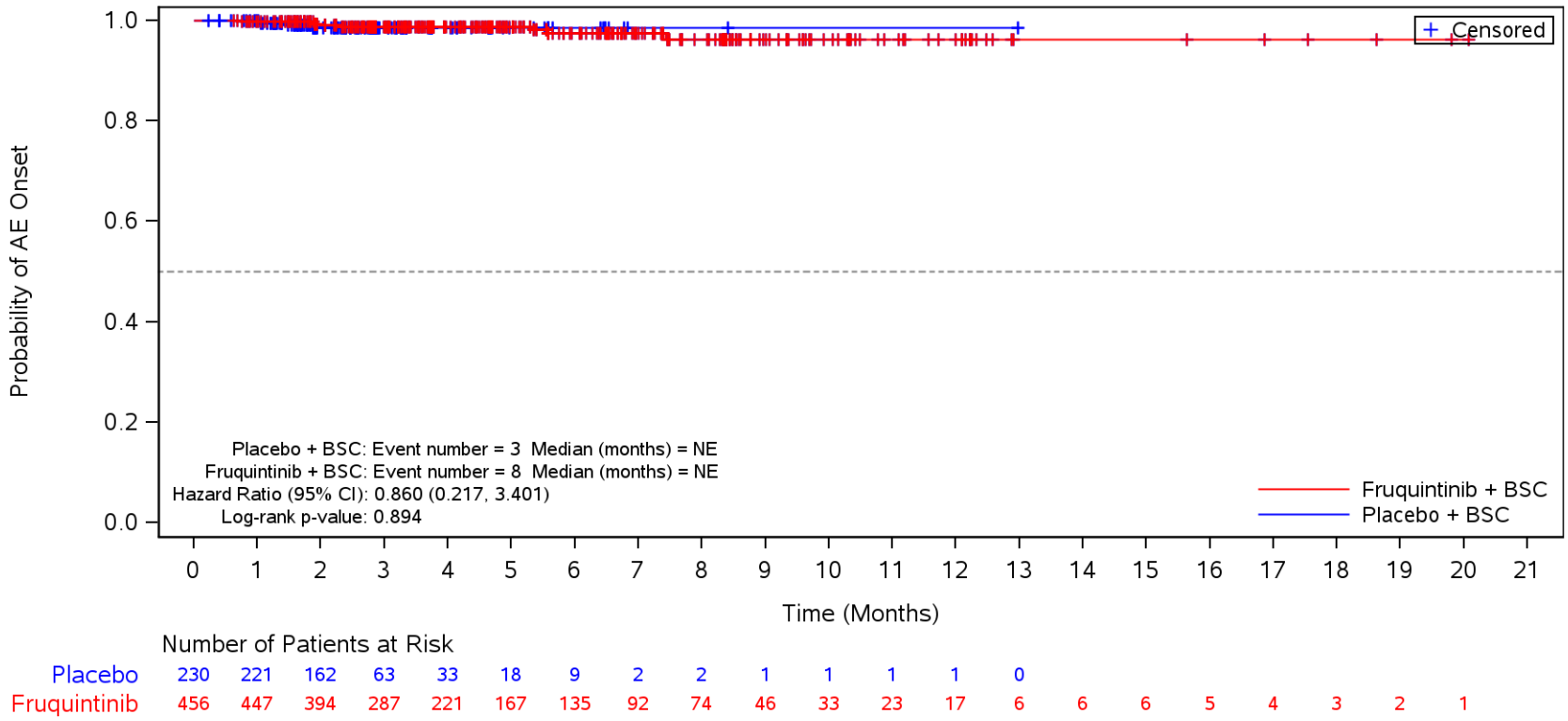
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≤ CTCAE Grade 2



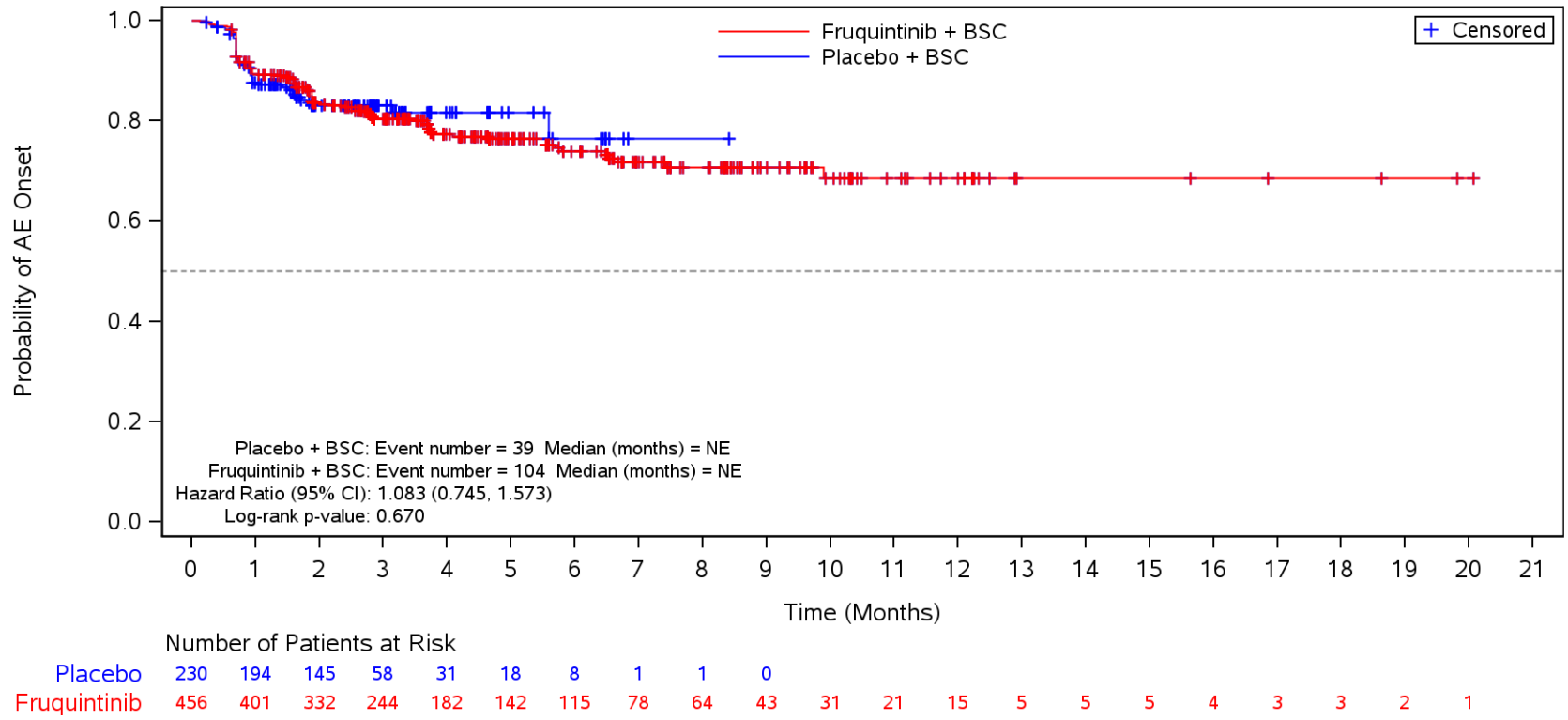
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≤ CTCAE Grade 2



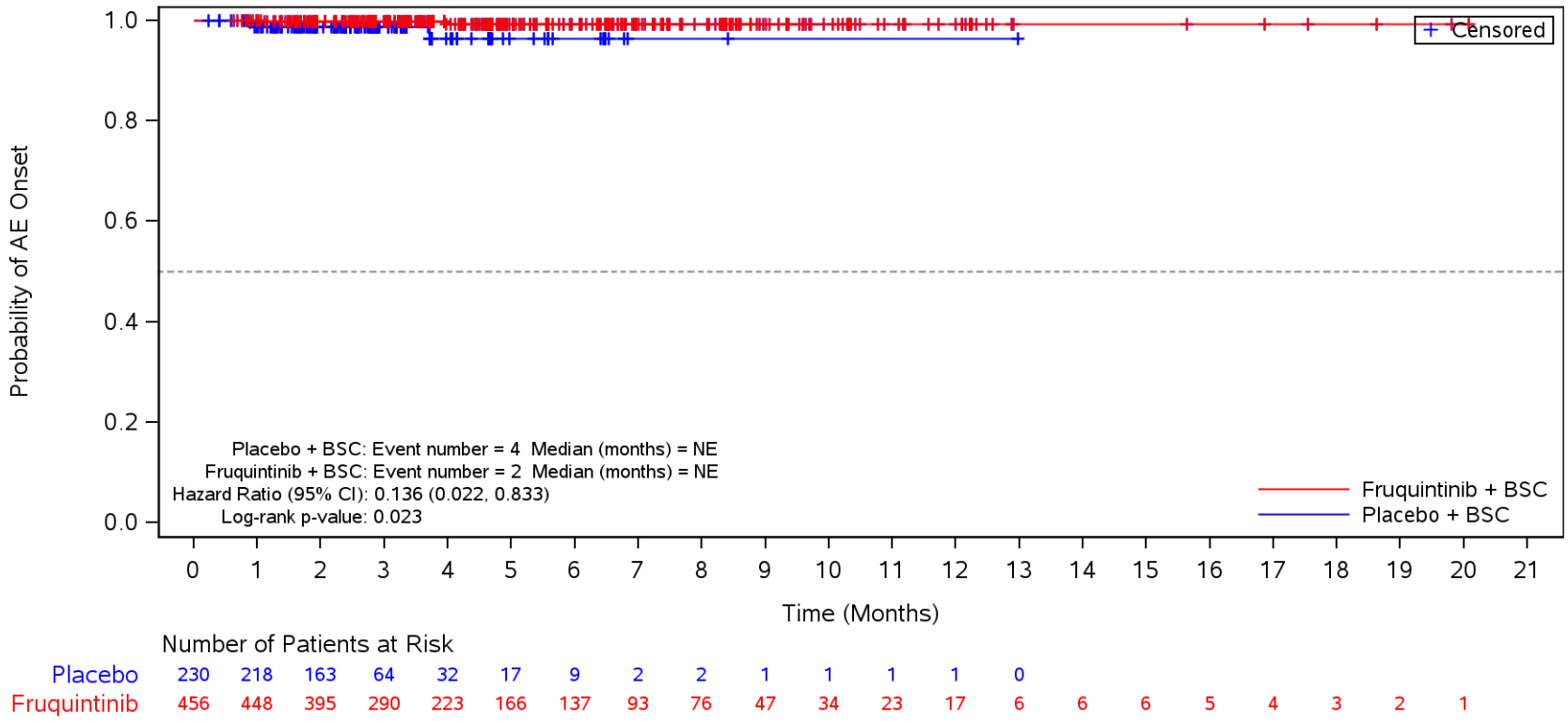
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≤ CTCAE Grade 2



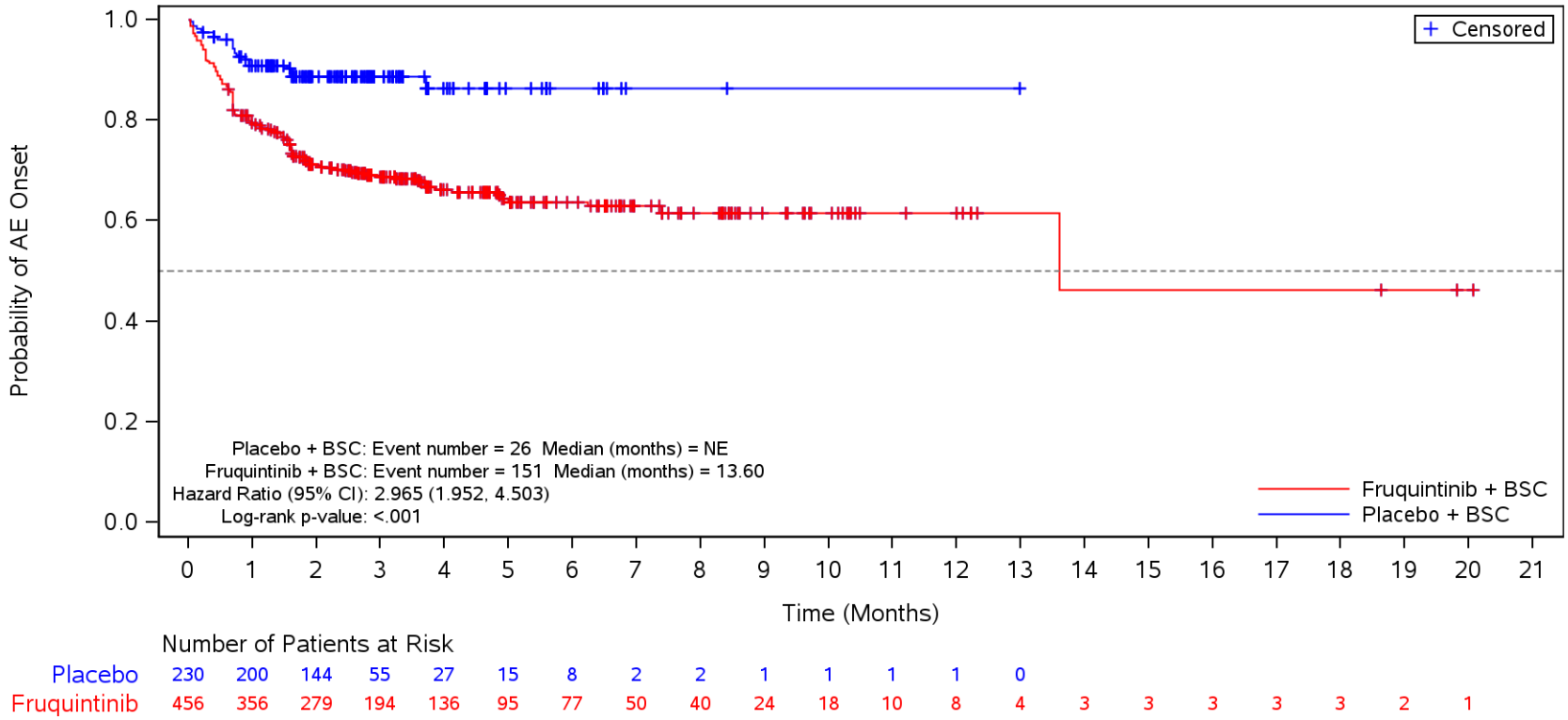
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≤ CTCAE Grade 2

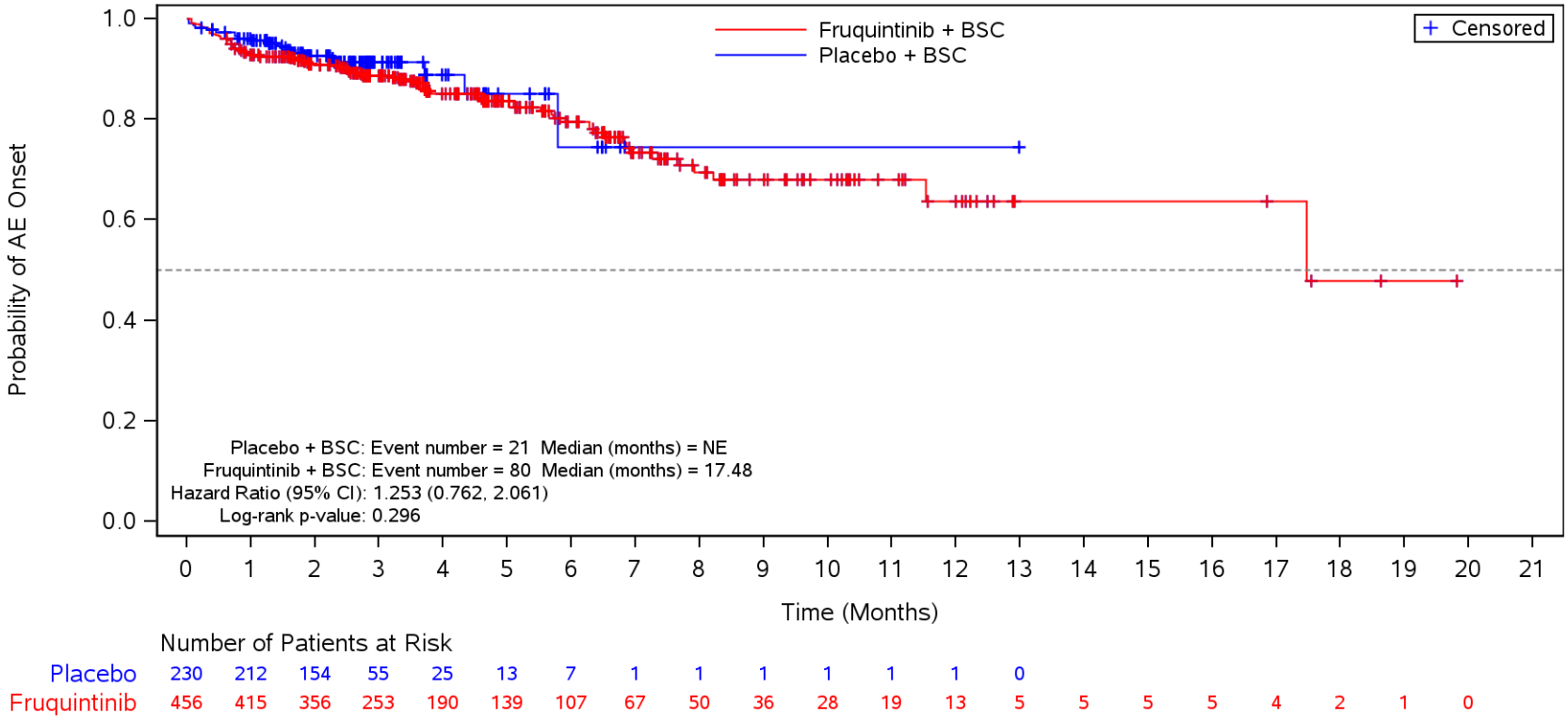


BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.5.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≤ CTCAE Grade 2



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.


Fruquintinib + BSC
Placebo + BSC
Censored
Probability of AE Onset
1.0
0.8
0.6
0.4
0.2
0.0
Placebo + BSC: Event number = 21 Median (months) = NE
Fruquintinib + BSC: Event number = 80 Median (months) = 17.48
Hazard Ratio (95% CI): 1.253 (0.762, 2.061)
Log-rank p-value: 0.296
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Time (Months)
Number of Patients at Risk
Placebo 230 212 154 55 25 13 7 1 1 1 1 1 1 0
Fruquintinib 456 415 356 253 190 139 107 67 50 36 28 19 13 5 5 5 5 4 2 1 0

2.1.8 AESI des NCI CTCAE-Grads ≥ 3

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	2 (0.4)
Number of Subjects Censored, n (%)	230 (100.0)	454 (99.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.602

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.7 (99.2, 100.0)
6 months	100.0 (100.0, 100.0)	99.3 (98.4, 100.0)
9 months	100.0 (100.0, 100.0)	99.3 (98.4, 100.0)
12 months	100.0 (100.0, 100.0)	99.3 (98.4, 100.0)
18 months	NE (NE, NE)	99.3 (98.4, 100.0)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	8 (1.8)
Number of Subjects Censored, n (%)	228 (99.1)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.798 (0.795)
95% CI		(0.379, 8.531)
Log-rank p-value		0.450

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	98.9 (97.4, 100.0)	98.4 (97.3, 99.6)
6 months	98.9 (97.4, 100.0)	98.1 (96.7, 99.4)
9 months	98.9 (97.4, 100.0)	98.1 (96.7, 99.4)
12 months	98.9 (97.4, 100.0)	98.1 (96.7, 99.4)
18 months	NE (NE, NE)	98.1 (96.7, 99.4)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	64 (14.0)
Number of Subjects Censored, n (%)	228 (99.1)	392 (86.0)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (10.35, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.0, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		16.621 (0.718)
95% CI		(4.066, 67.942)
Log-rank p-value		<.001

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.8, 100.0)	86.1 (82.8, 89.3)
6 months	99.1 (97.8, 100.0)	85.5 (82.2, 88.9)
9 months	99.1 (97.8, 100.0)	85.5 (82.2, 88.9)
12 months	99.1 (97.8, 100.0)	82.1 (74.8, 89.4)
18 months	NE (NE, NE)	82.1 (74.8, 89.4)
Median Follow-up Time (months)	2.83	3.50

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	8 (1.8)
Number of Subjects Censored, n (%)	226 (98.3)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.489 (0.645)
95% CI		(0.138, 1.730)
Log-rank p-value		0.309

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	99.0 (98.0, 100.0)
6 months	93.5 (85.5, 100.0)	97.7 (95.9, 99.5)
9 months	93.5 (85.5, 100.0)	96.3 (93.1, 99.5)
12 months	93.5 (85.5, 100.0)	96.3 (93.1, 99.5)
18 months	NE (NE, NE)	96.3 (93.1, 99.5)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	10 (2.2)
Number of Subjects Censored, n (%)	229 (99.6)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.707 (1.073)
95% CI		(0.330, 22.192)
Log-rank p-value		0.313

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.4 (98.1, 100.0)	98.9 (97.9, 99.9)
6 months	99.4 (98.1, 100.0)	97.2 (95.0, 99.4)
9 months	99.4 (98.1, 100.0)	94.1 (89.3, 98.9)
12 months	99.4 (98.1, 100.0)	94.1 (89.3, 98.9)
18 months	NE (NE, NE)	94.1 (89.3, 98.9)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	14 (3.1)
Number of Subjects Censored, n (%)	228 (99.1)	442 (96.9)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		2.091 (0.772)
95% CI		(0.461, 9.493)
Log-rank p-value		0.316

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.6, 100.0)	98.4 (97.2, 99.6)
6 months	97.3 (93.0, 100.0)	95.5 (92.8, 98.1)
9 months	97.3 (93.0, 100.0)	95.5 (92.8, 98.1)
12 months	97.3 (93.0, 100.0)	93.0 (87.5, 98.5)
18 months	NE (NE, NE)	93.0 (87.5, 98.5)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	21 (9.1)	38 (8.3)
Number of Subjects Censored, n (%)	209 (90.9)	418 (91.7)
Time to first TEAE (months)		
25% percentile (95% CI)	10.18 (NE, NE)	NE (NE, NE)
Median (95% CI)	10.18 (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	10.18 (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 10.2	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.672 (0.280)
95% CI		(0.388, 1.163)
Log-rank p-value		0.139

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	90.9 (87.0, 94.7)	93.5 (91.2, 95.8)
6 months	90.9 (87.0, 94.7)	90.2 (86.9, 93.5)
9 months	90.9 (87.0, 94.7)	88.3 (84.0, 92.5)
12 months	0.0 (NE, NE)	85.9 (79.7, 92.0)
18 months	0.0 (NE, NE)	85.9 (79.7, 92.0)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	4 (0.9)
Number of Subjects Censored, n (%)	228 (99.1)	452 (99.1)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.805 (0.879)
95% CI		(0.144, 4.506)
Log-rank p-value		0.781

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	99.3 (98.5, 100.0)
6 months	99.1 (97.9, 100.0)	98.9 (97.8, 100.0)
9 months	99.1 (97.9, 100.0)	98.9 (97.8, 100.0)
12 months	99.1 (97.9, 100.0)	98.9 (97.8, 100.0)
18 months	NE (NE, NE)	98.9 (97.8, 100.0)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	31 (6.8)
Number of Subjects Censored, n (%)	229 (99.6)	425 (93.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	13.14 (13.14, NE)
Median (95% CI)	NE (NE, NE)	NE (13.14, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		11.778 (1.019)
95% CI		(1.597, 86.838)
Log-rank p-value		0.002

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	94.9 (92.8, 97.0)
6 months	99.6 (98.7, 100.0)	90.8 (87.2, 94.4)
9 months	99.6 (98.7, 100.0)	89.7 (85.5, 93.9)
12 months	99.6 (98.7, 100.0)	89.7 (85.5, 93.9)
18 months	NE (NE, NE)	67.3 (29.1, 100.0)
Median Follow-up Time (months)	2.83	3.71

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	13 (5.7)	30 (6.6)
Number of Subjects Censored, n (%)	217 (94.3)	426 (93.4)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.802 (0.343)
95% CI		(0.410, 1.571)
Log-rank p-value		0.560

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.7.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
TEAE ≥ CTCAE Grade 3

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	94.9 (92.0, 97.9)	94.4 (92.2, 96.7)
6 months	90.3 (83.0, 97.5)	91.3 (87.8, 94.8)
9 months	90.3 (83.0, 97.5)	88.8 (84.1, 93.6)
12 months	90.3 (83.0, 97.5)	88.8 (84.1, 93.6)
18 months	NE (NE, NE)	88.8 (84.1, 93.6)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

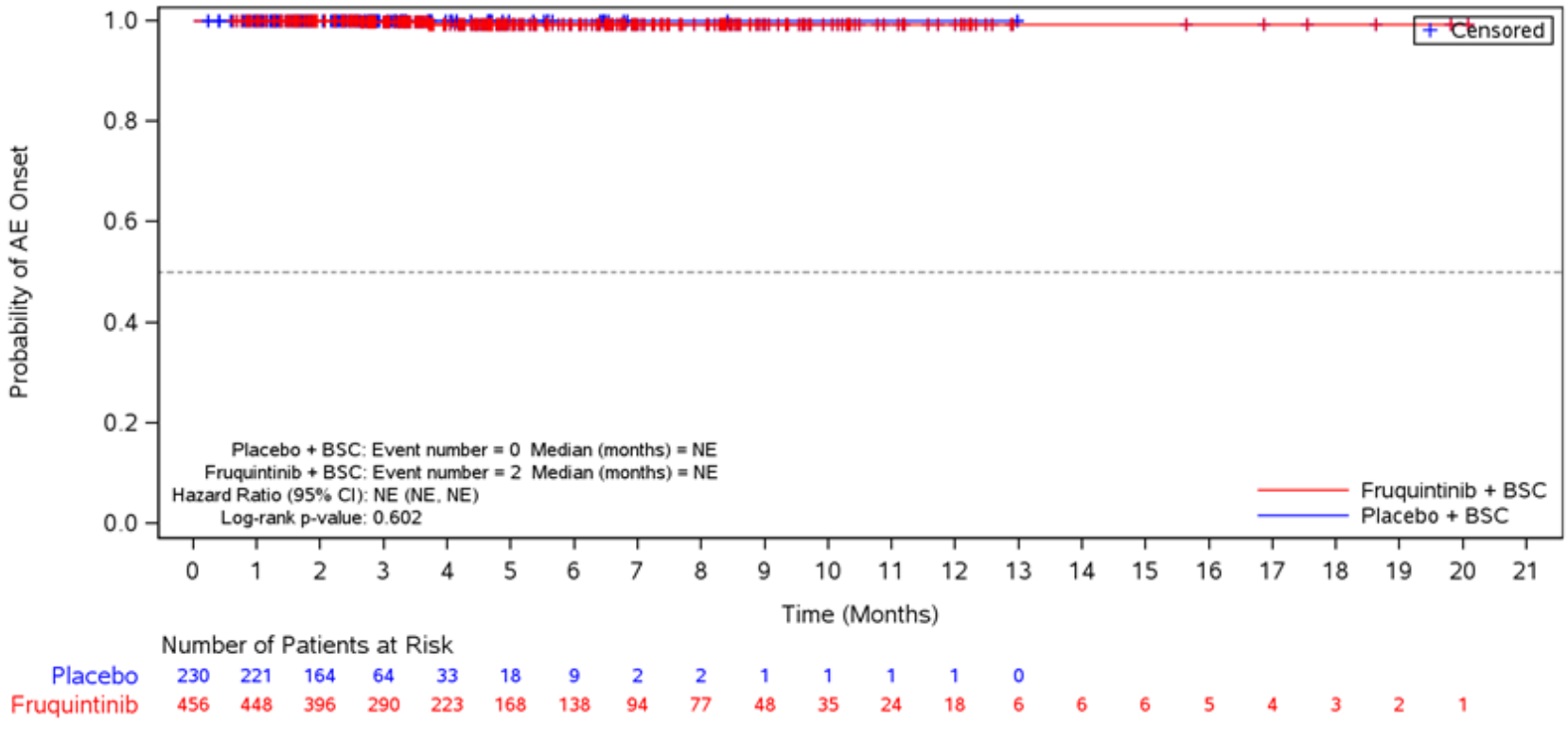
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

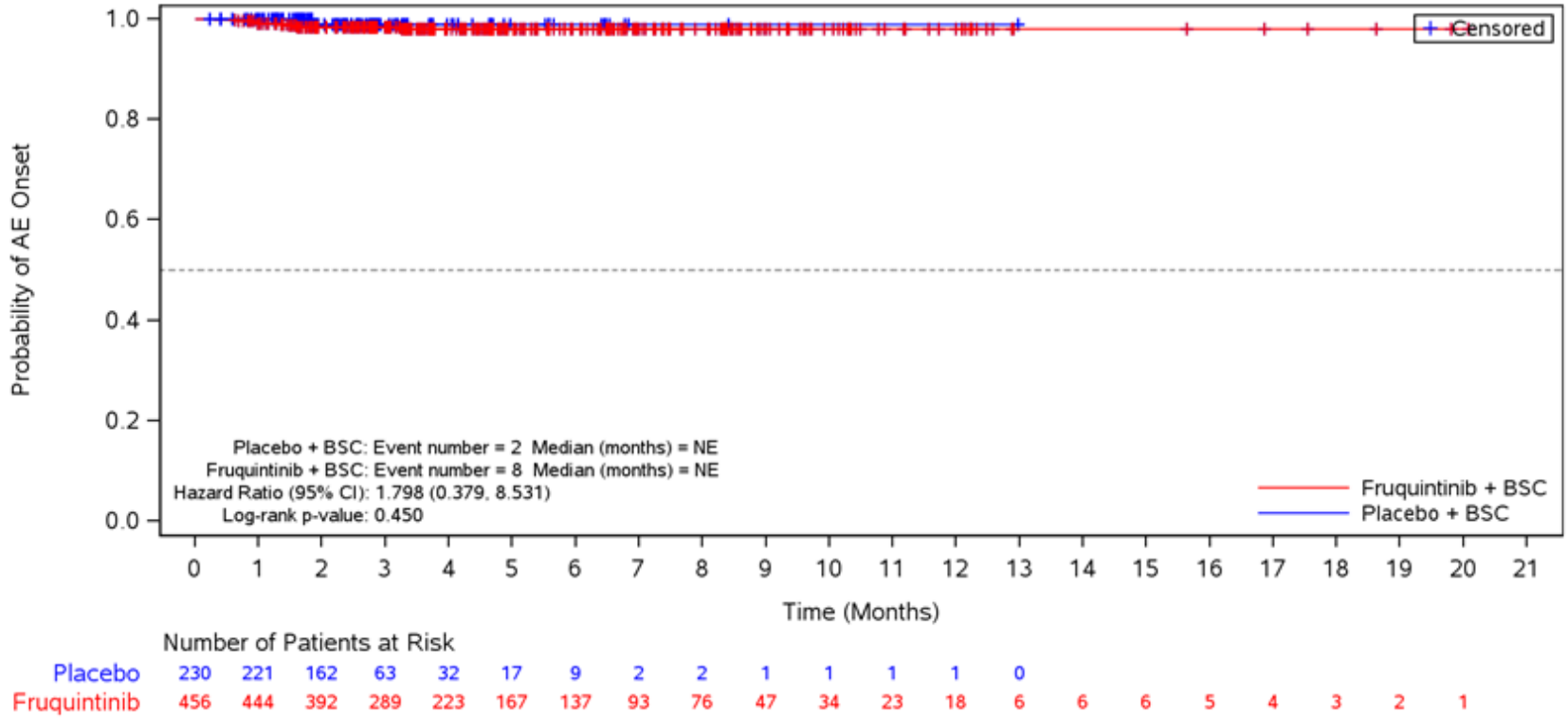
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≥ CTCAE Grade 3



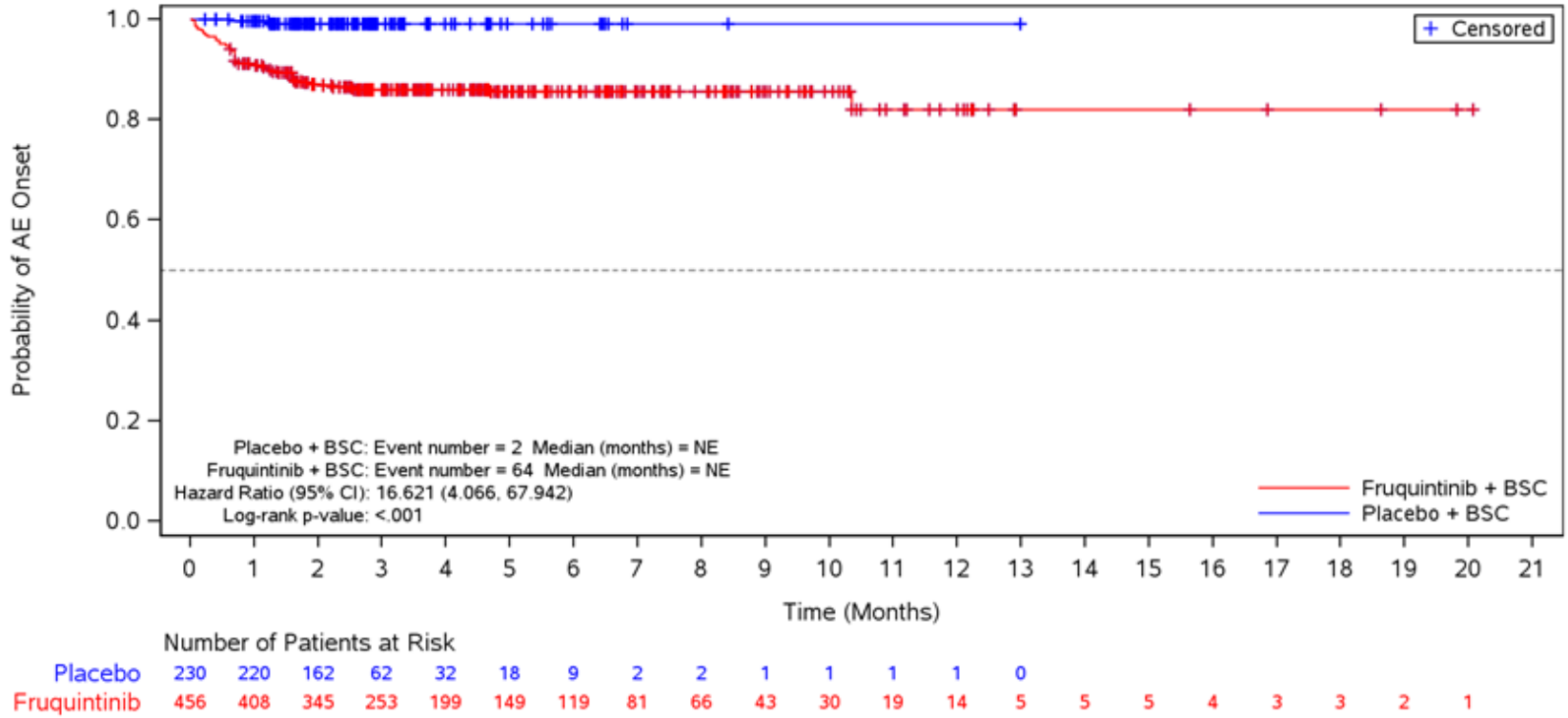
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≥ CTCAE Grade 3



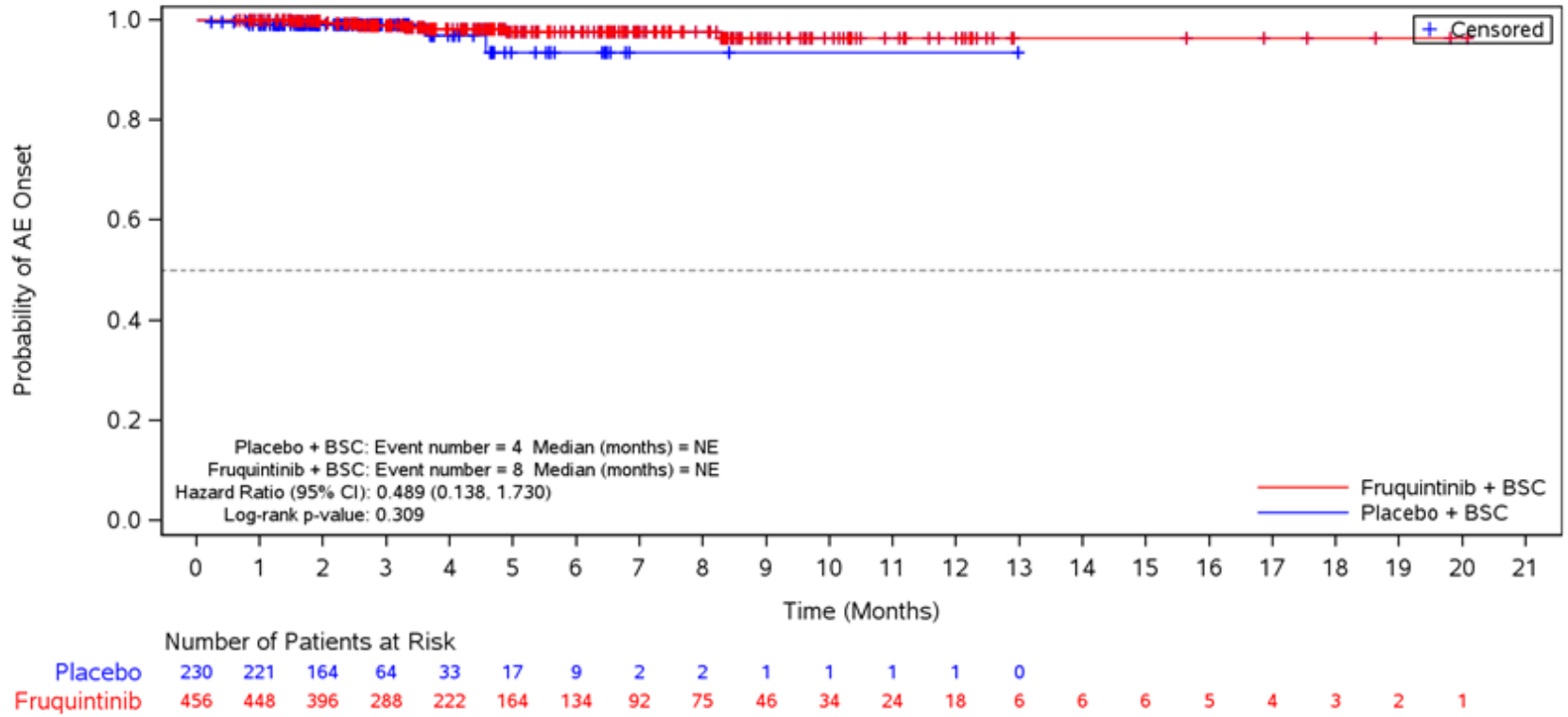
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≥ CTCAE Grade 3



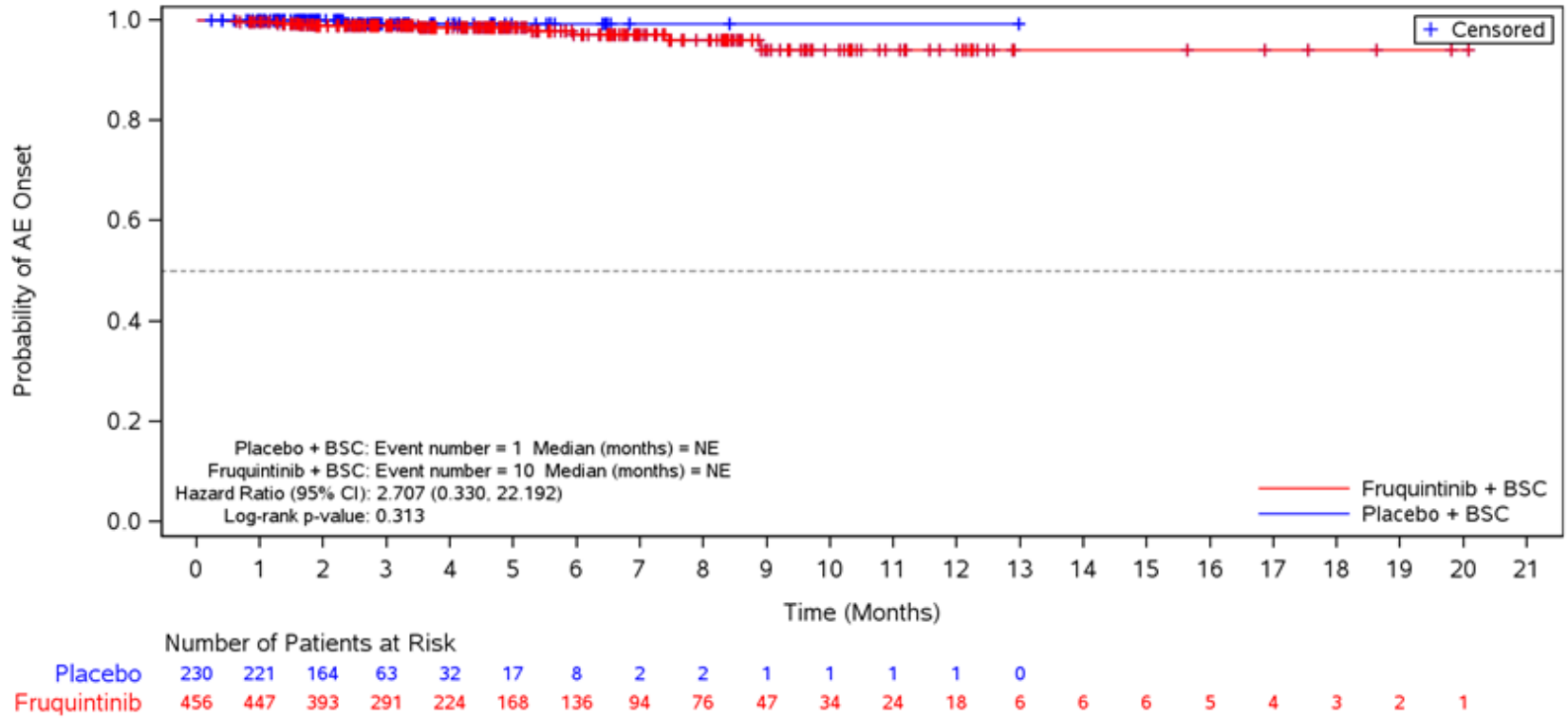
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≥ CTCAE Grade 3



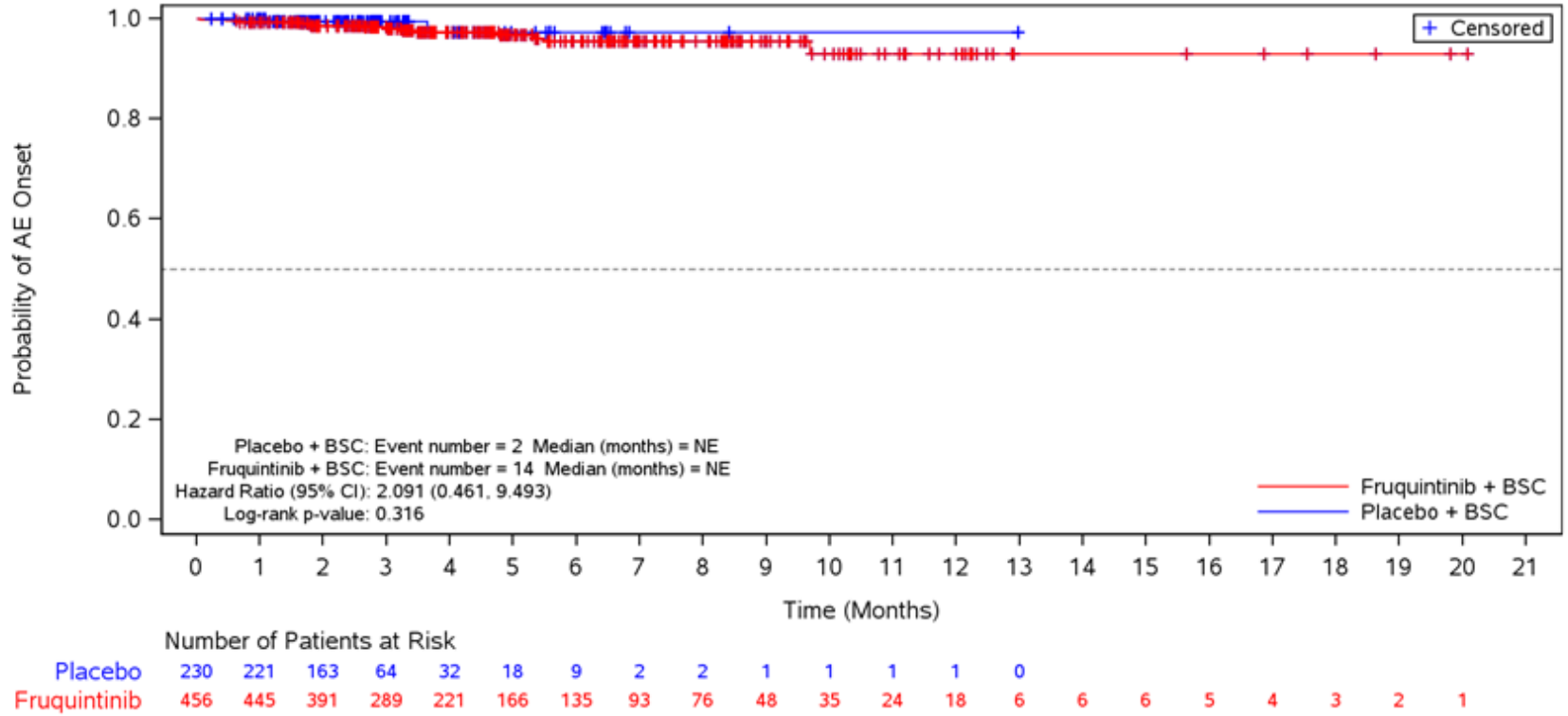
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≥ CTCAE Grade 3



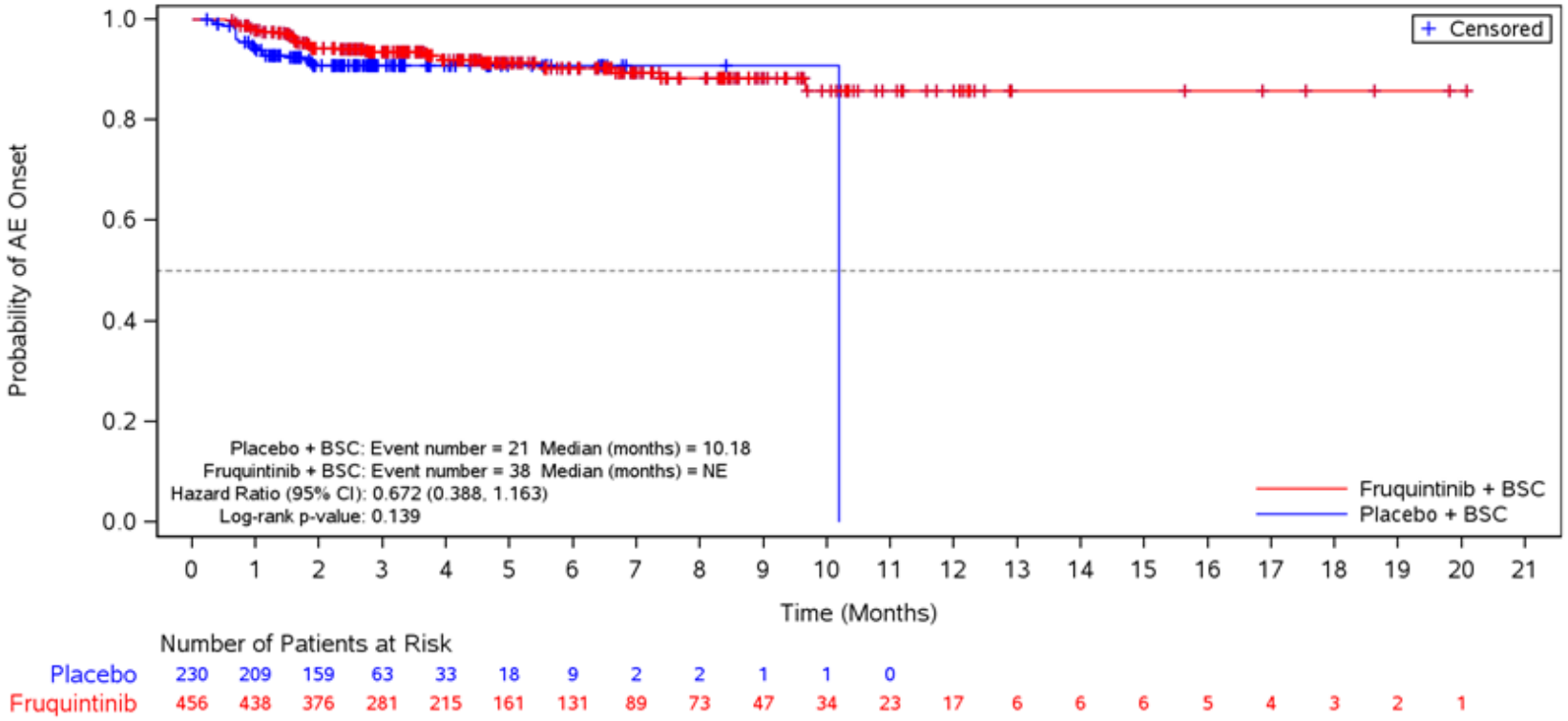
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≥ CTCAE Grade 3



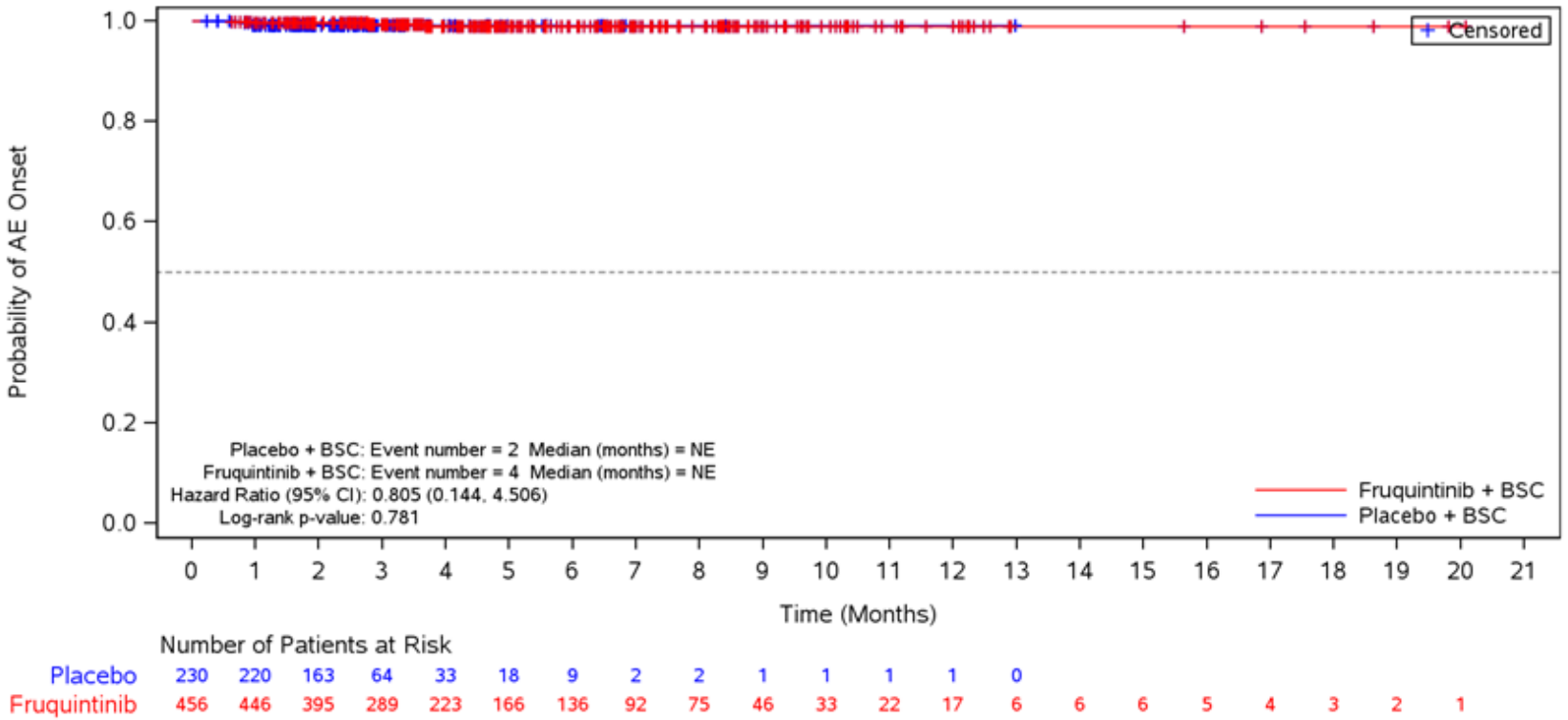
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≥ CTCAE Grade 3



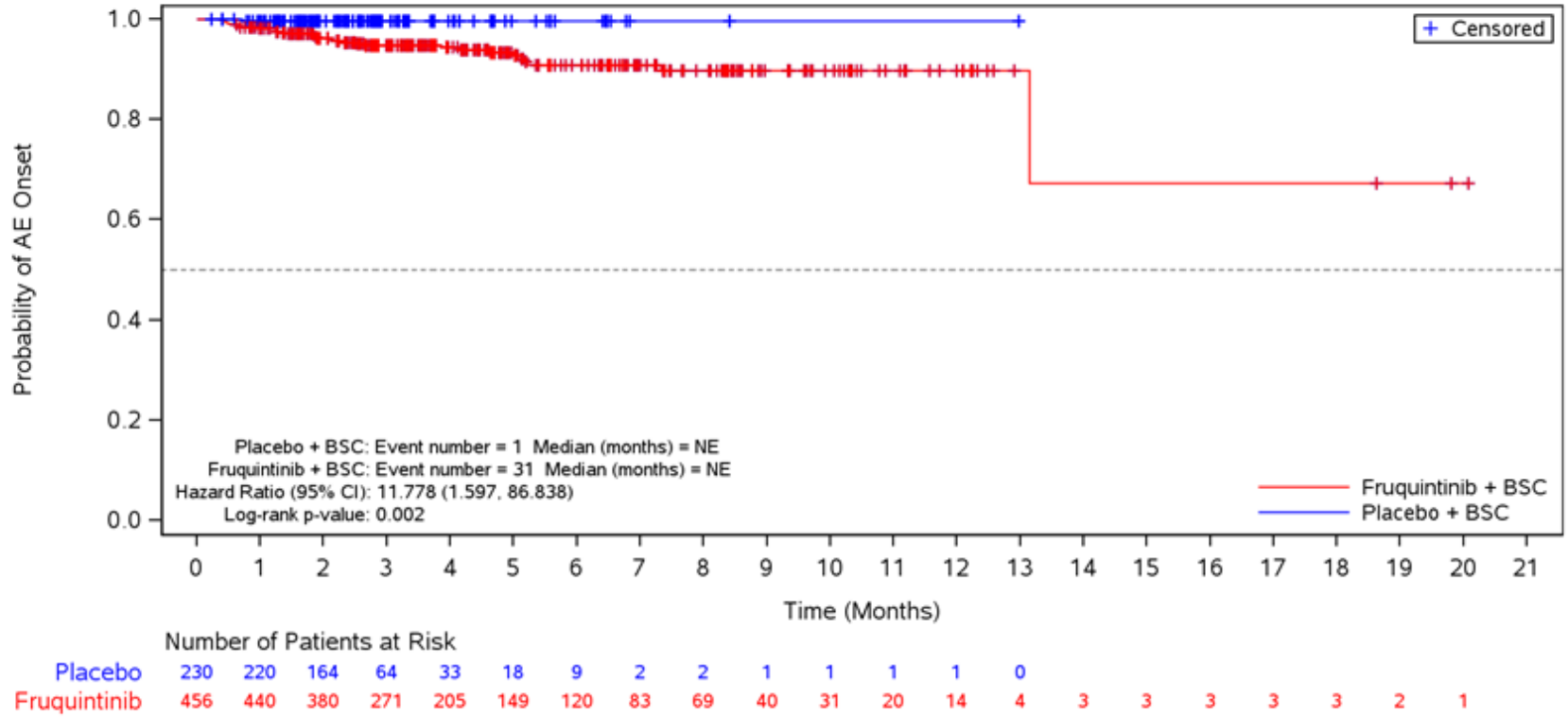
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≥ CTCAE Grade 3



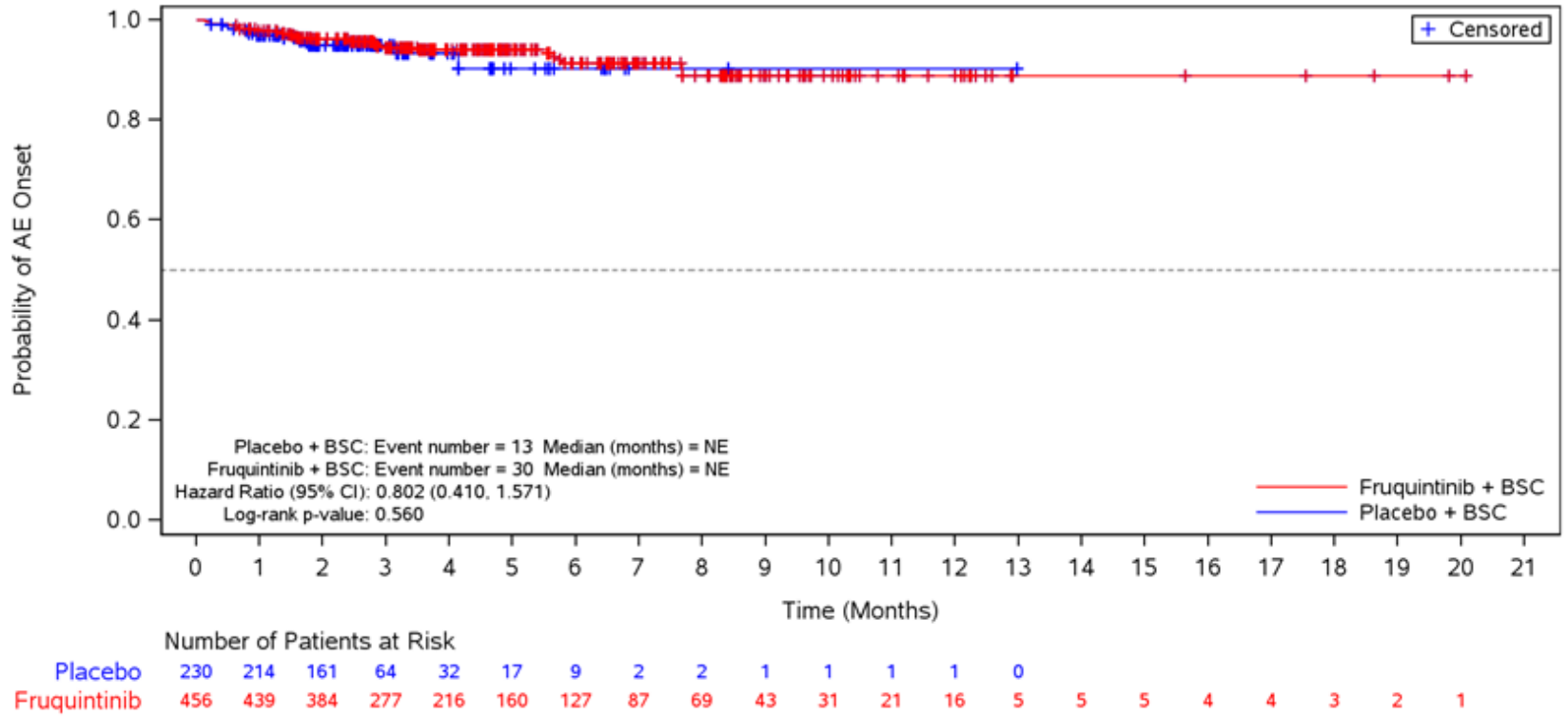
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≥ CTCAE Grade 3



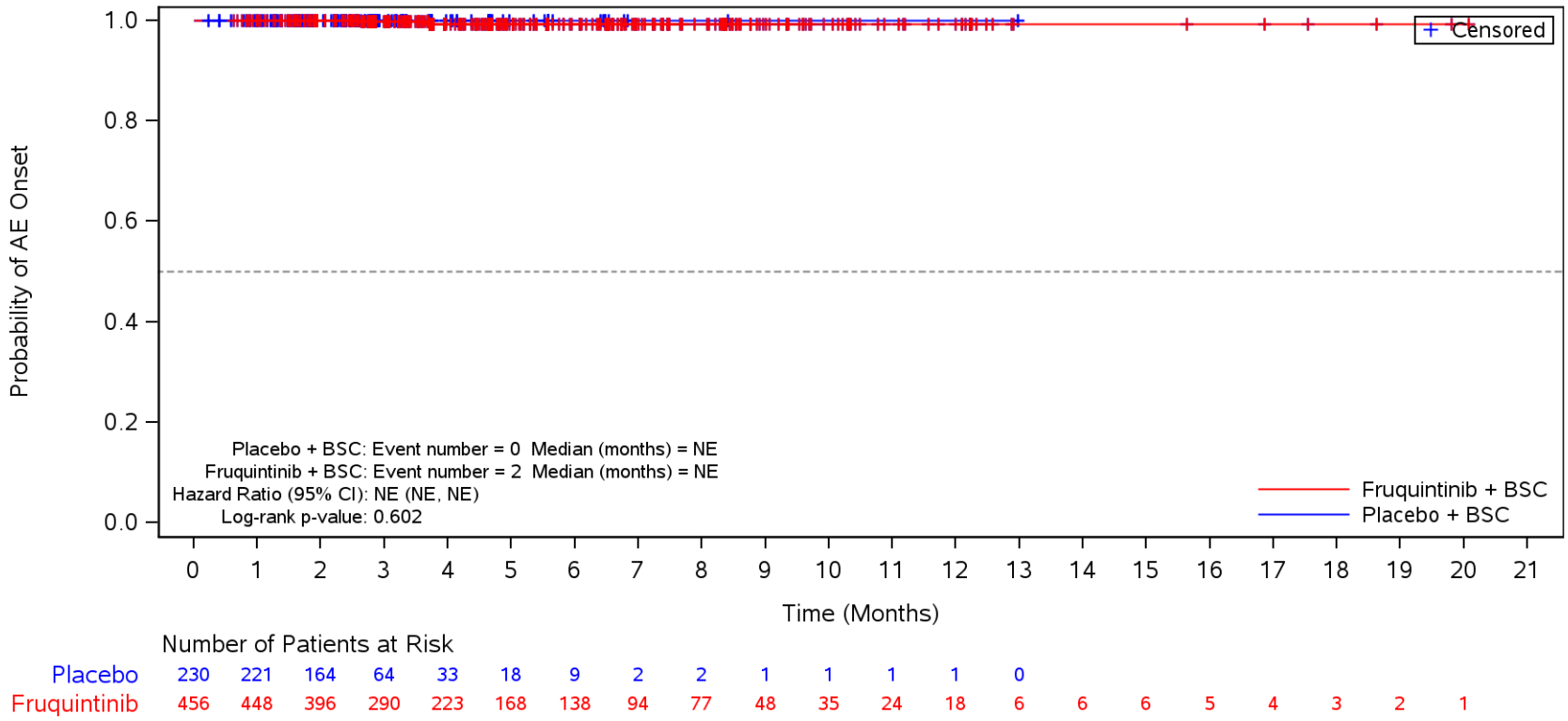
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Infections
Safety Population
TEAE ≥ CTCAE Grade 3



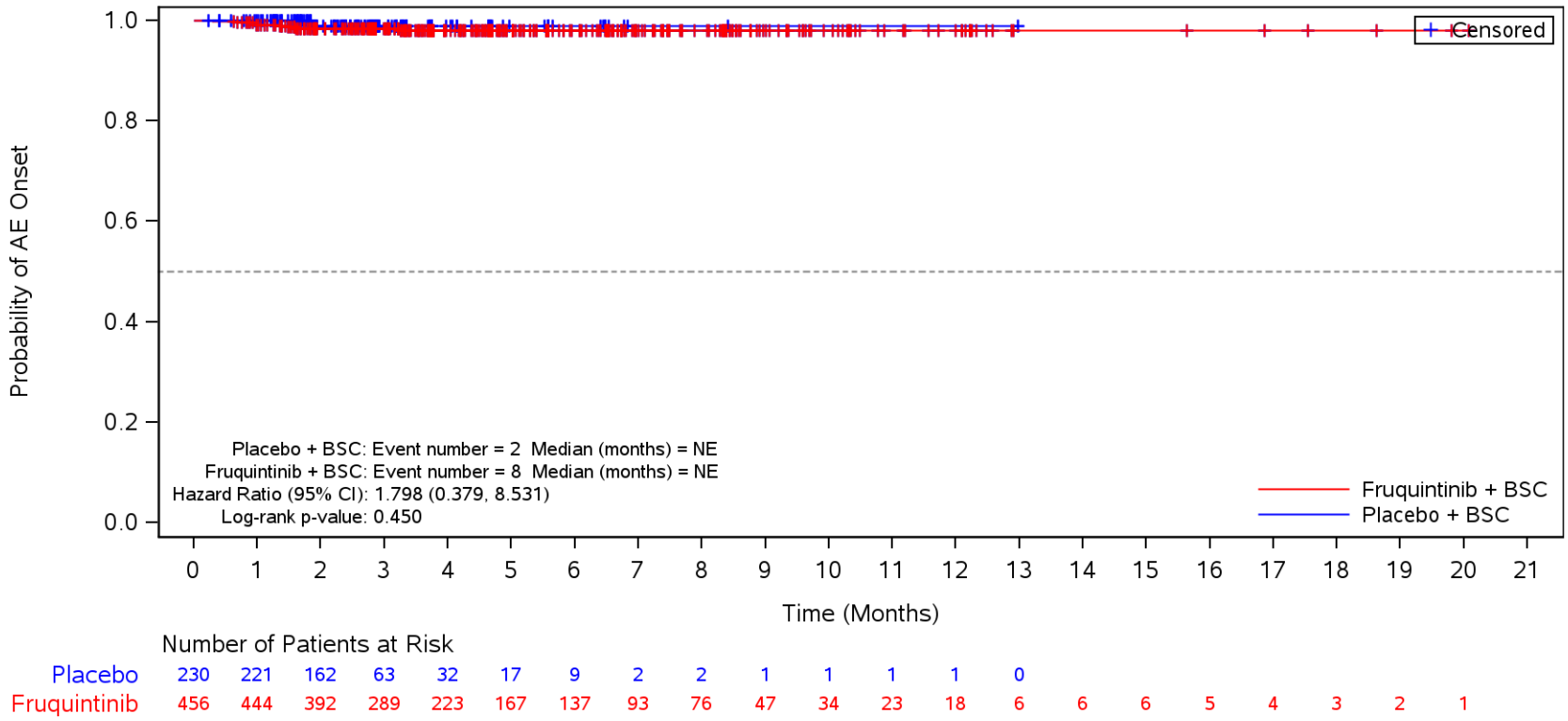
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
TEAE ≥ CTCAE Grade 3



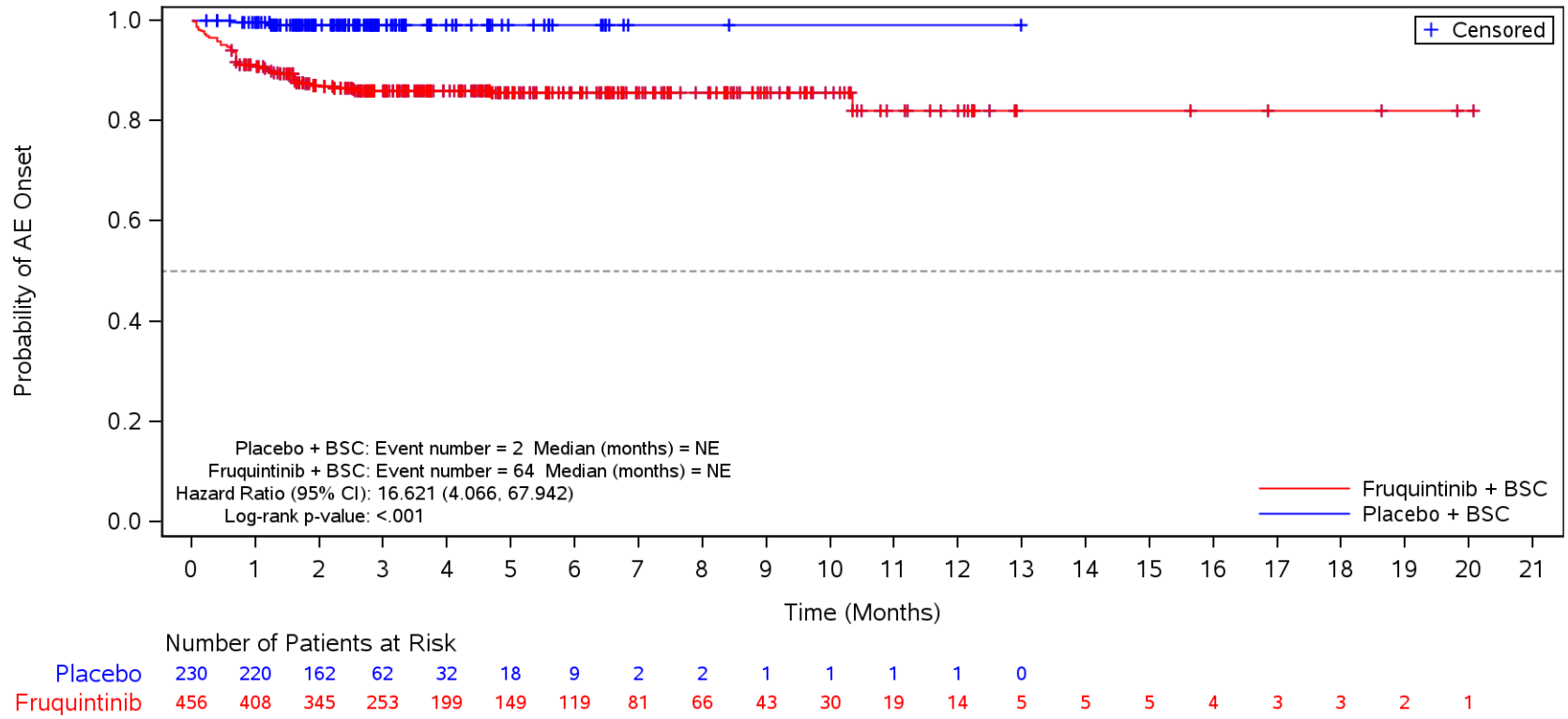
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
TEAE ≥ CTCAE Grade 3



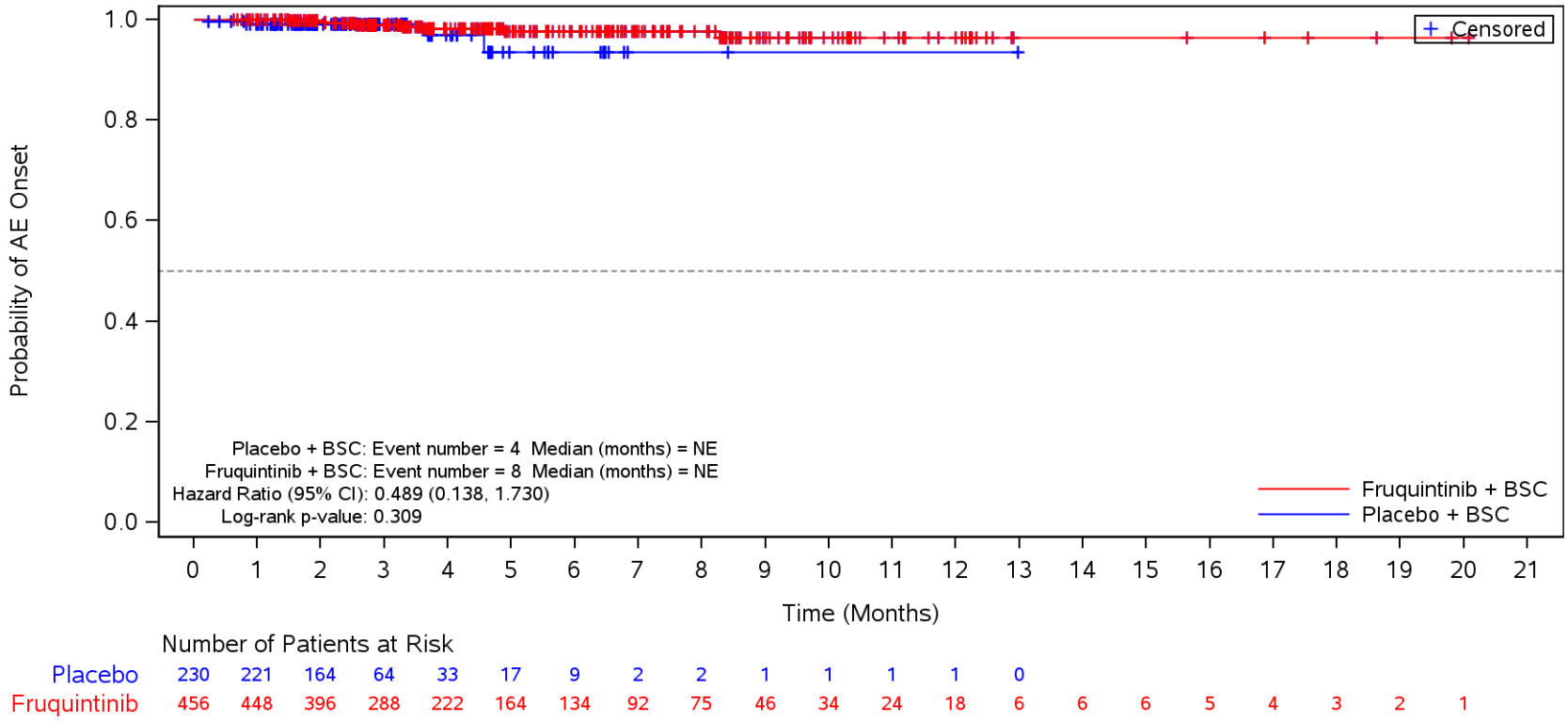
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
TEAE ≥ CTCAE Grade 3



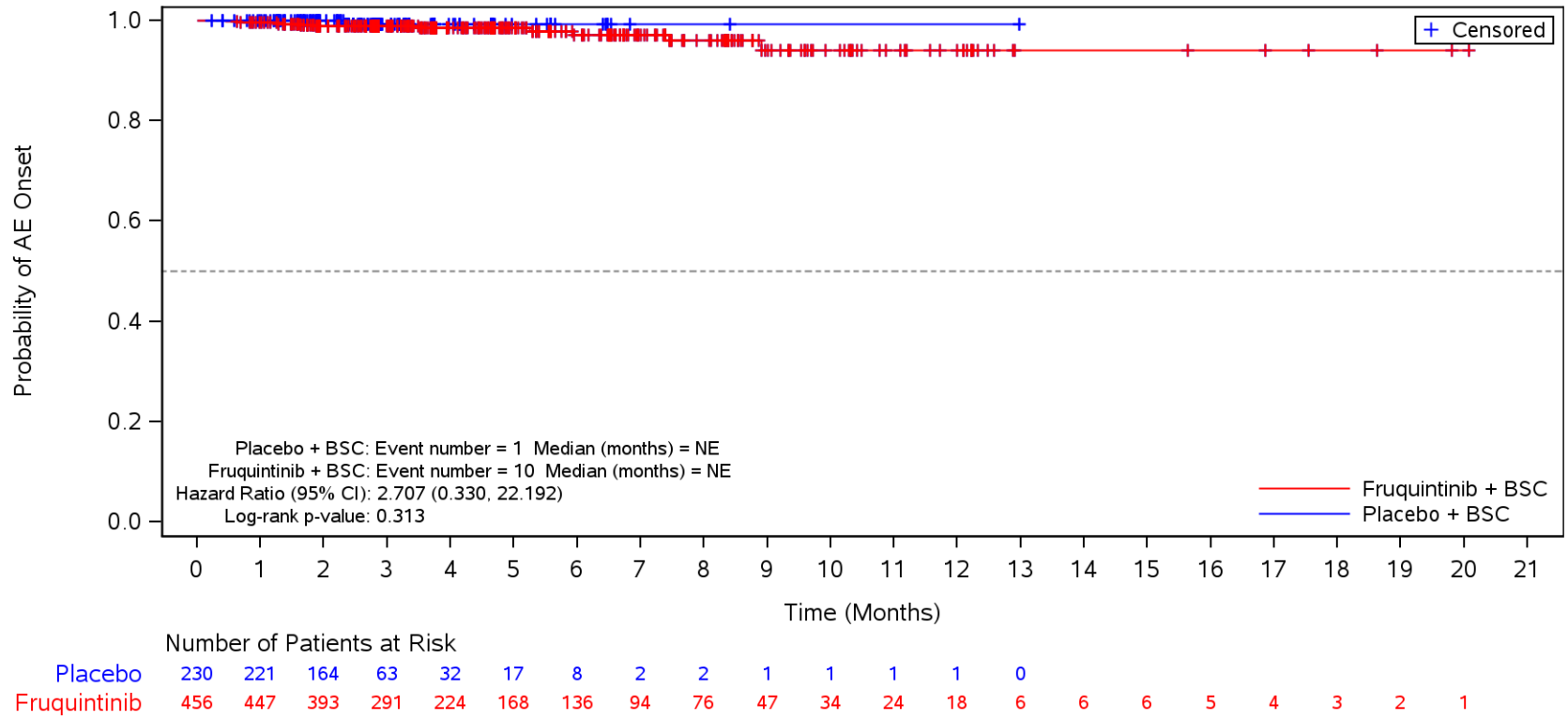
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
TEAE ≥ CTCAE Grade 3



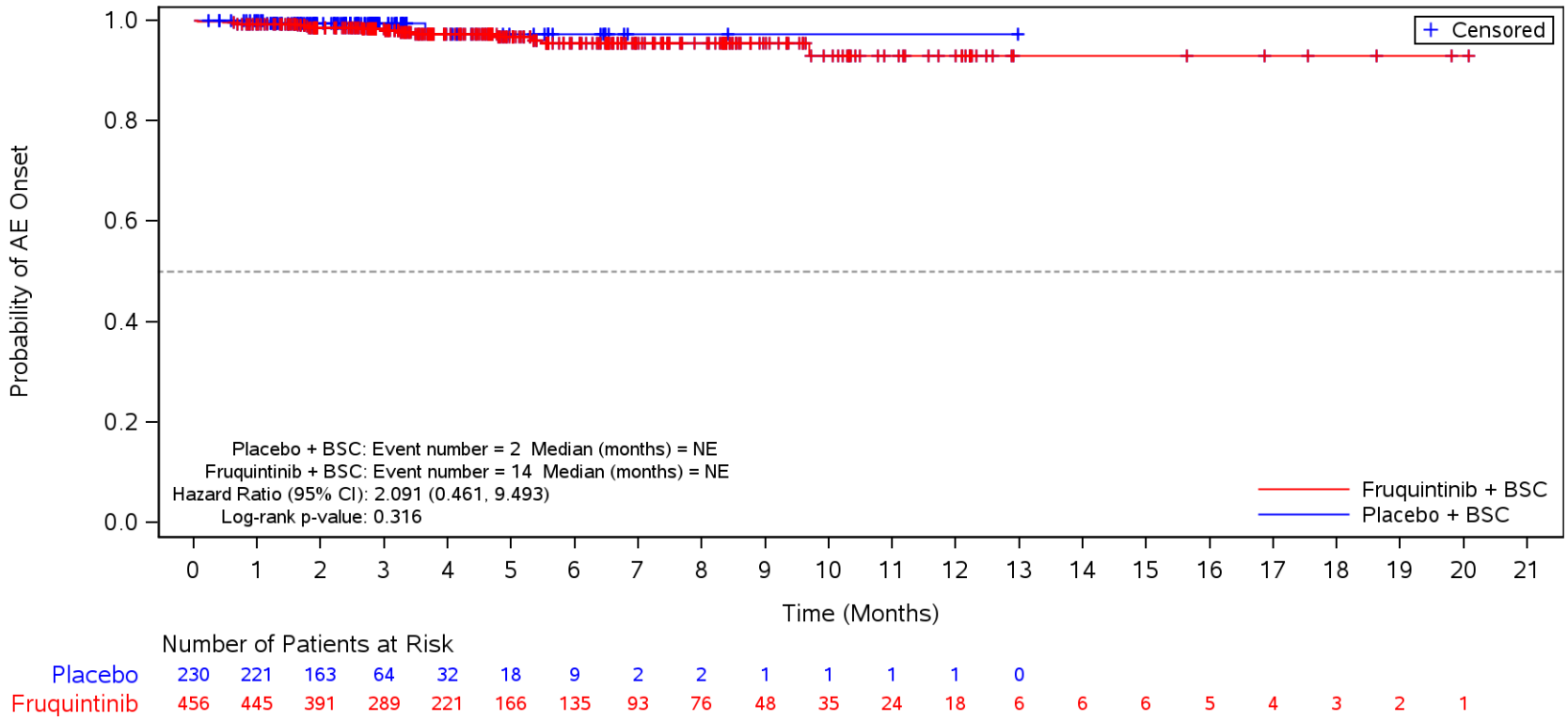
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
TEAE ≥ CTCAE Grade 3



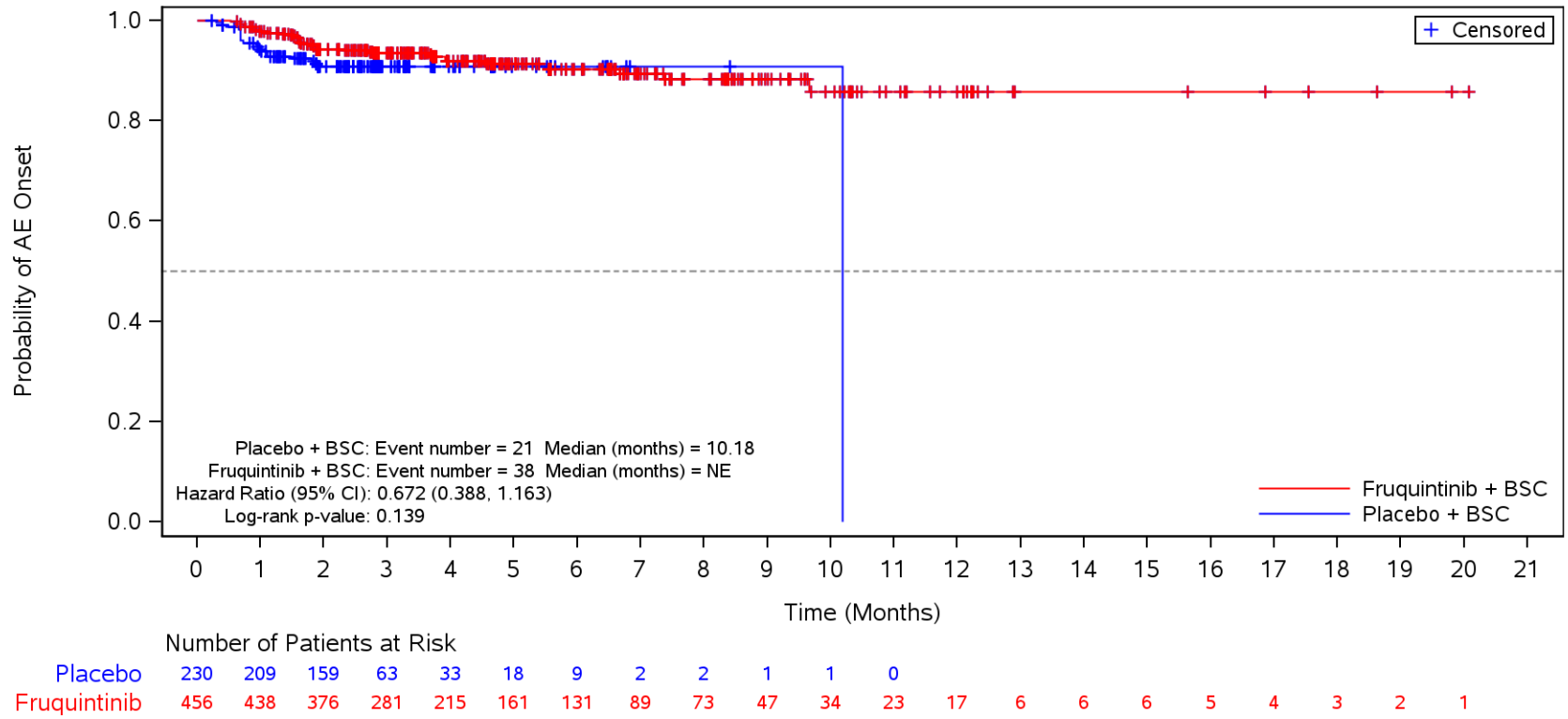
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
TEAE ≥ CTCAE Grade 3



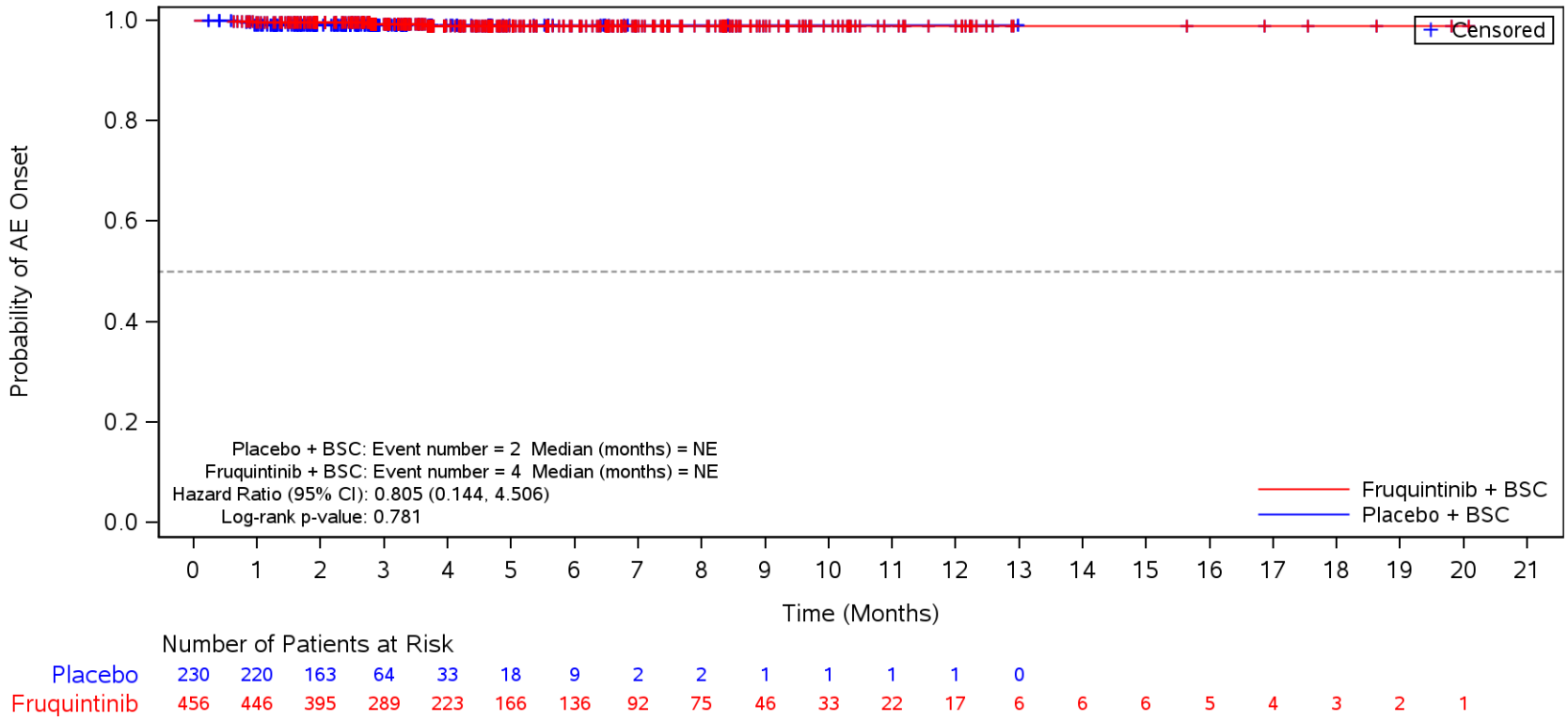
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
TEAE ≥ CTCAE Grade 3



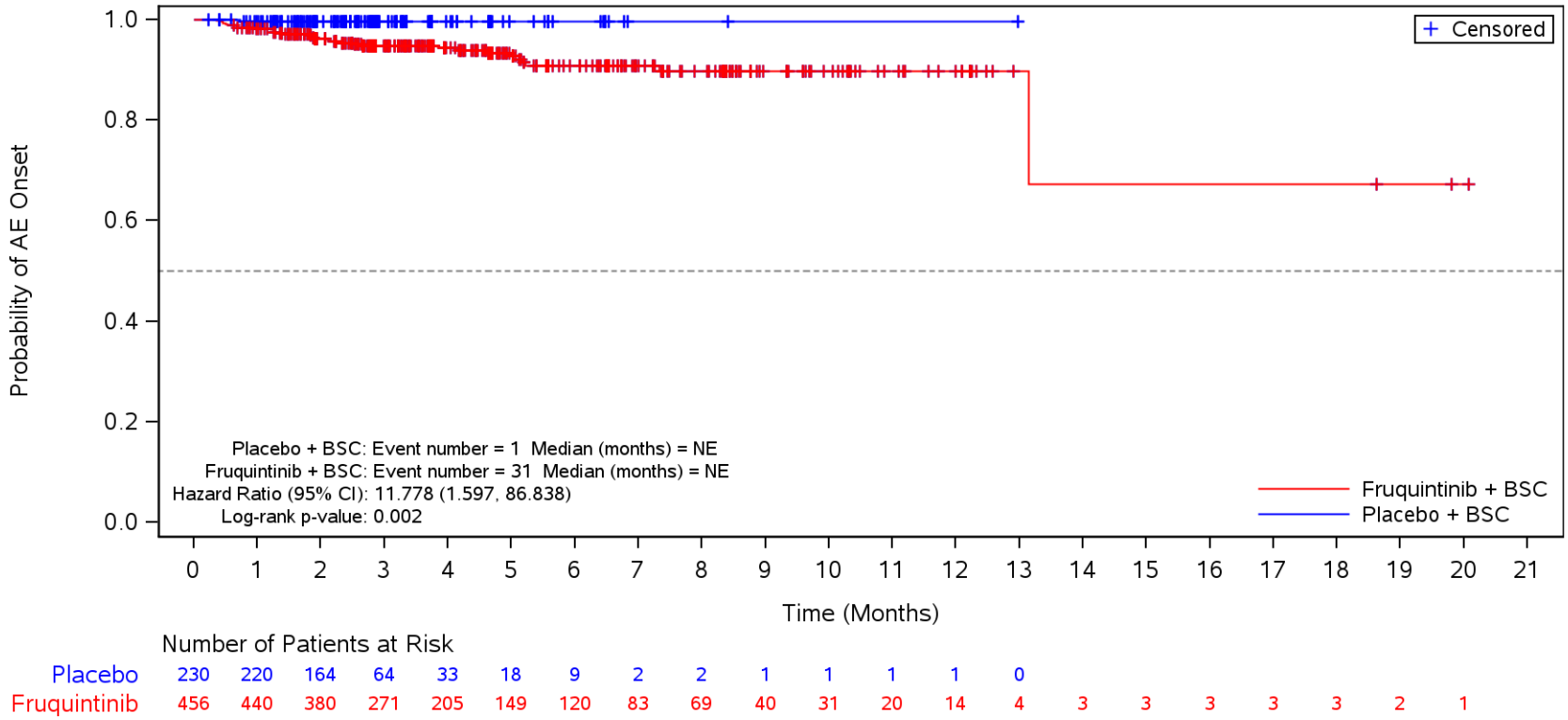
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
TEAE ≥ CTCAE Grade 3

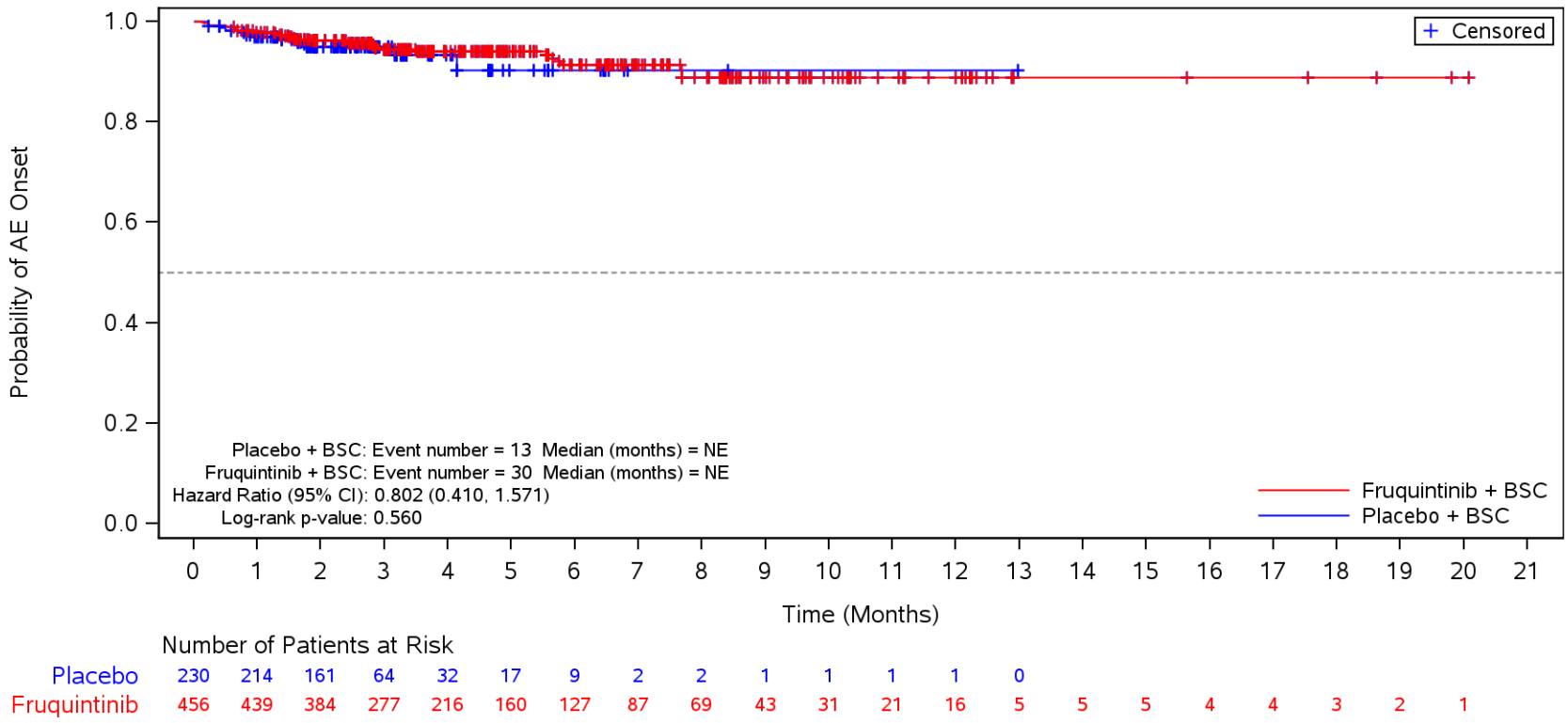


BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.7.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
TEAE ≥ CTCAE Grade 3



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.


Probability of AE Onset
1.0
0.8
0.6
0.4
0.2
0.0
Censored
Placebo + BSC: Event number = 13 Median (months) = NE
Fruquintinib + BSC: Event number = 30 Median (months) = NE
Hazard Ratio (95% CI): 0.802 (0.410, 1.571)
Log-rank p-value: 0.560
Fruquintinib + BSC
Placebo + BSC
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Time (Months)
Number of Patients at Risk
Placebo 230 214 161 64 32 17 9 2 2 1 1 1 1 0
Fruquintinib 456 439 384 277 216 160 127 87 69 43 31 21 16 5 5 5 4 4 3 2 1

2.1.9 Schwerwiegende AESI

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	1 (0.2)
Number of Subjects Censored, n (%)	230 (100.0)	455 (99.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.495

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
18 months	NE (NE, NE)	99.8 (99.3, 100.0)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	1 (0.2)
Number of Subjects Censored, n (%)	230 (100.0)	455 (99.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.523

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
18 months	NE (NE, NE)	99.8 (99.3, 100.0)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	8 (1.8)
Number of Subjects Censored, n (%)	230 (100.0)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.050

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
6 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
9 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
12 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
18 months	NE (NE, NE)	98.2 (97.0, 99.4)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	10 (2.2)
Number of Subjects Censored, n (%)	226 (98.3)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.686 (0.615)
95% CI		(0.206, 2.286)
Log-rank p-value		0.598

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	98.5 (97.3, 99.7)
6 months	93.5 (85.5, 100.0)	97.2 (95.3, 99.1)
9 months	93.5 (85.5, 100.0)	95.8 (92.6, 99.1)
12 months	93.5 (85.5, 100.0)	95.8 (92.6, 99.1)
18 months	NE (NE, NE)	95.8 (92.6, 99.1)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	11 (2.4)
Number of Subjects Censored, n (%)	229 (99.6)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		3.260 (1.064)
95% CI		(0.405, 26.228)
Log-rank p-value		0.222

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.4 (98.1, 100.0)	98.6 (97.6, 99.7)
6 months	99.4 (98.1, 100.0)	96.9 (94.7, 99.2)
9 months	99.4 (98.1, 100.0)	93.9 (89.1, 98.7)
12 months	99.4 (98.1, 100.0)	93.9 (89.1, 98.7)
18 months	NE (NE, NE)	93.9 (89.1, 98.7)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	8 (1.8)
Number of Subjects Censored, n (%)	228 (99.1)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.158 (0.819)
95% CI		(0.232, 5.765)
Log-rank p-value		0.827

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.6, 100.0)	99.1 (98.2, 100.0)
6 months	97.3 (93.0, 100.0)	97.7 (95.9, 99.5)
9 months	97.3 (93.0, 100.0)	97.7 (95.9, 99.5)
12 months	97.3 (93.0, 100.0)	95.2 (89.9, 100.0)
18 months	NE (NE, NE)	95.2 (89.9, 100.0)
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	11 (2.4)
Number of Subjects Censored, n (%)	219 (95.2)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.425 (0.433)
95% CI		(0.182, 0.994)
Log-rank p-value		0.041

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.1 (92.3, 97.9)	97.7 (96.3, 99.1)
6 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
9 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
12 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
18 months	NE (NE, NE)	97.0 (95.1, 98.9)
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	3 (0.7)
Number of Subjects Censored, n (%)	229 (99.6)	453 (99.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.089 (1.174)
95% CI		(0.109, 10.874)
Log-rank p-value		0.996

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	99.5 (98.8, 100.0)
6 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
9 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
12 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
18 months	NE (NE, NE)	99.1 (98.0, 100.0)
Median Follow-up Time (months)	2.83	3.88

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	2 (0.4)
Number of Subjects Censored, n (%)	230 (100.0)	454 (99.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Median (95% CI)	NE (NE, NE)	NE (13.14, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)
Log-rank p-value		0.471

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
18 months	NE (NE, NE)	83.2 (53.4, 100.0)
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	25 (5.5)
Number of Subjects Censored, n (%)	218 (94.8)	431 (94.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.695 (0.366)
95% CI		(0.339, 1.425)
Log-rank p-value		0.379

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.4 (92.6, 98.2)	95.7 (93.7, 97.7)
6 months	90.7 (83.5, 97.9)	93.2 (90.1, 96.3)
9 months	90.7 (83.5, 97.9)	90.0 (85.3, 94.7)
12 months	90.7 (83.5, 97.9)	90.0 (85.3, 94.7)
18 months	NE (NE, NE)	90.0 (85.3, 94.7)
Median Follow-up Time (months)	2.83	3.75

* indicates censored value.

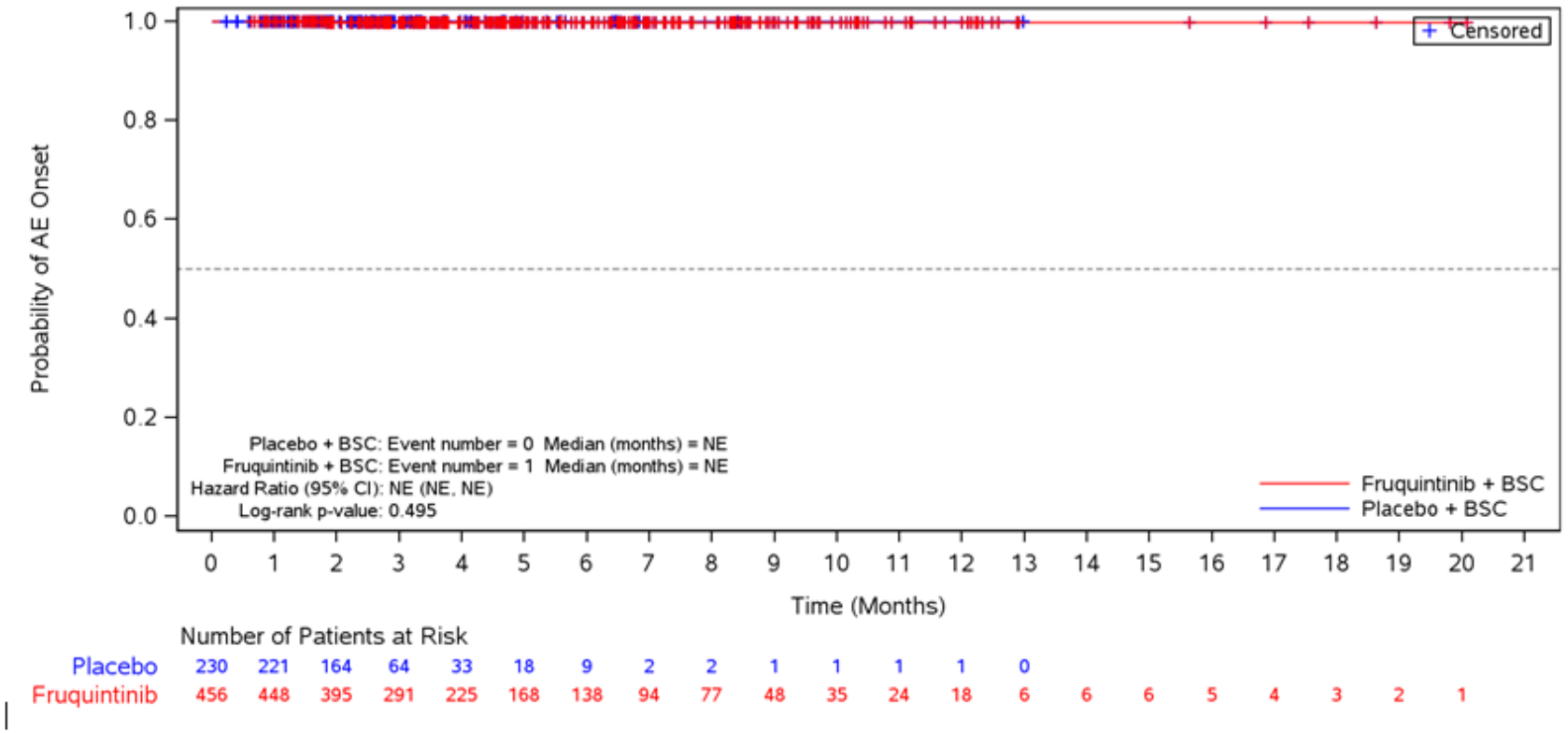
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

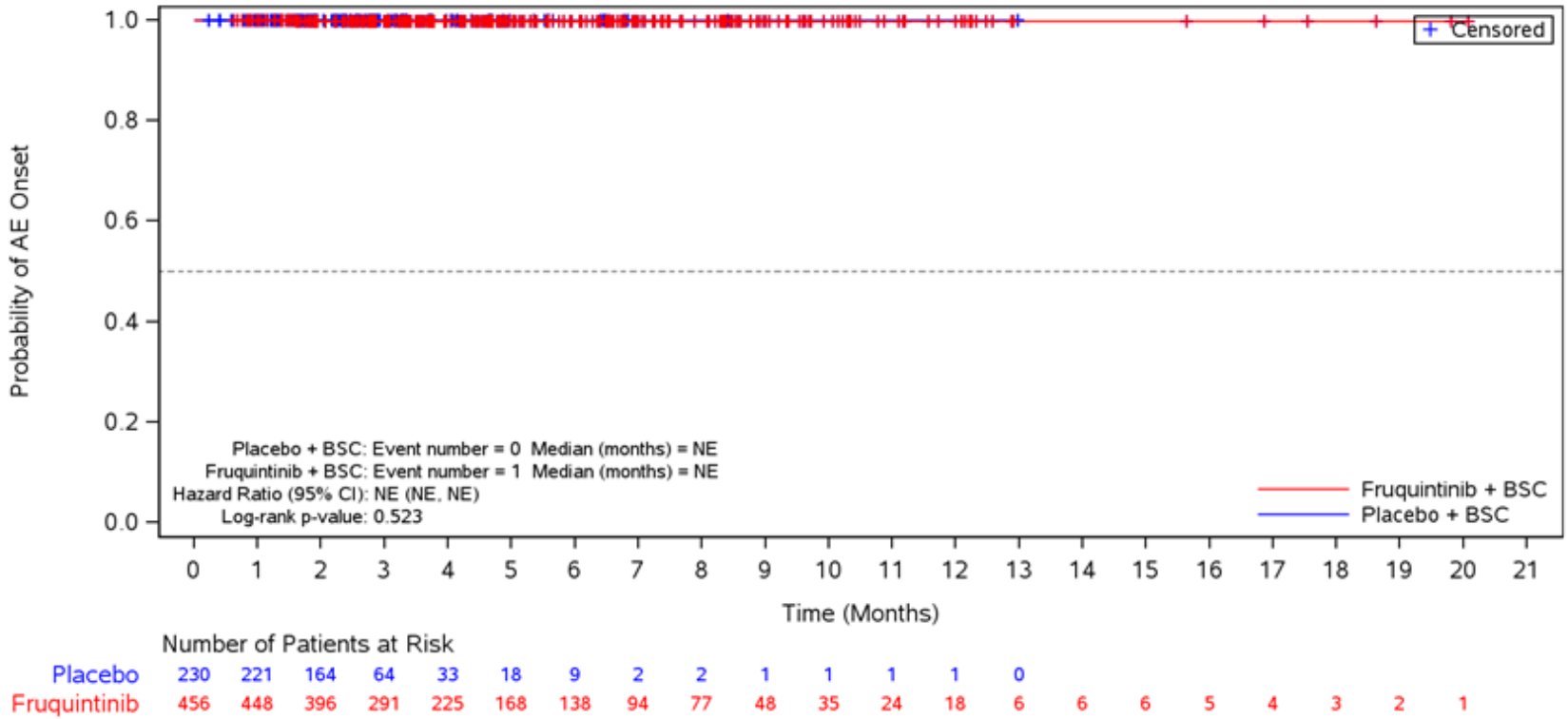
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE



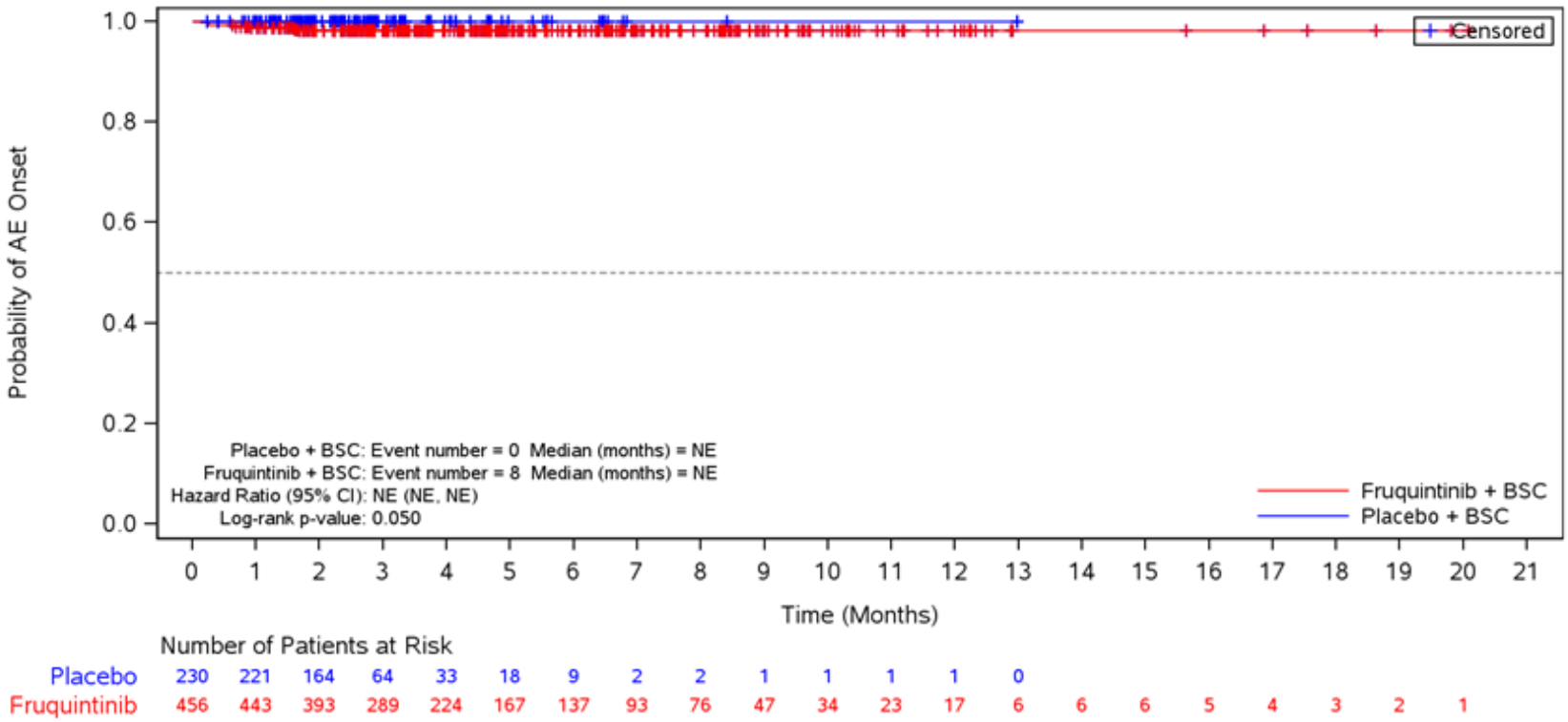
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE



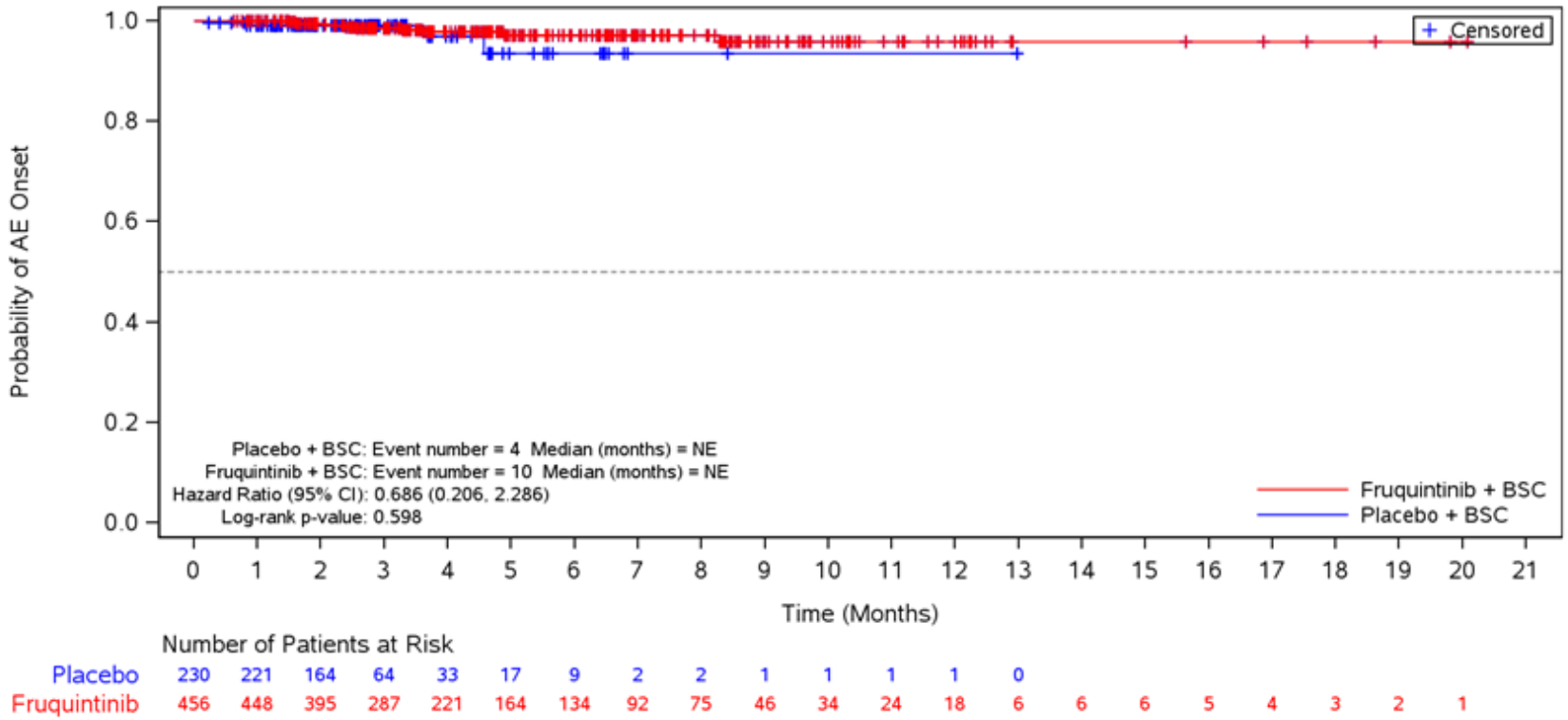
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE



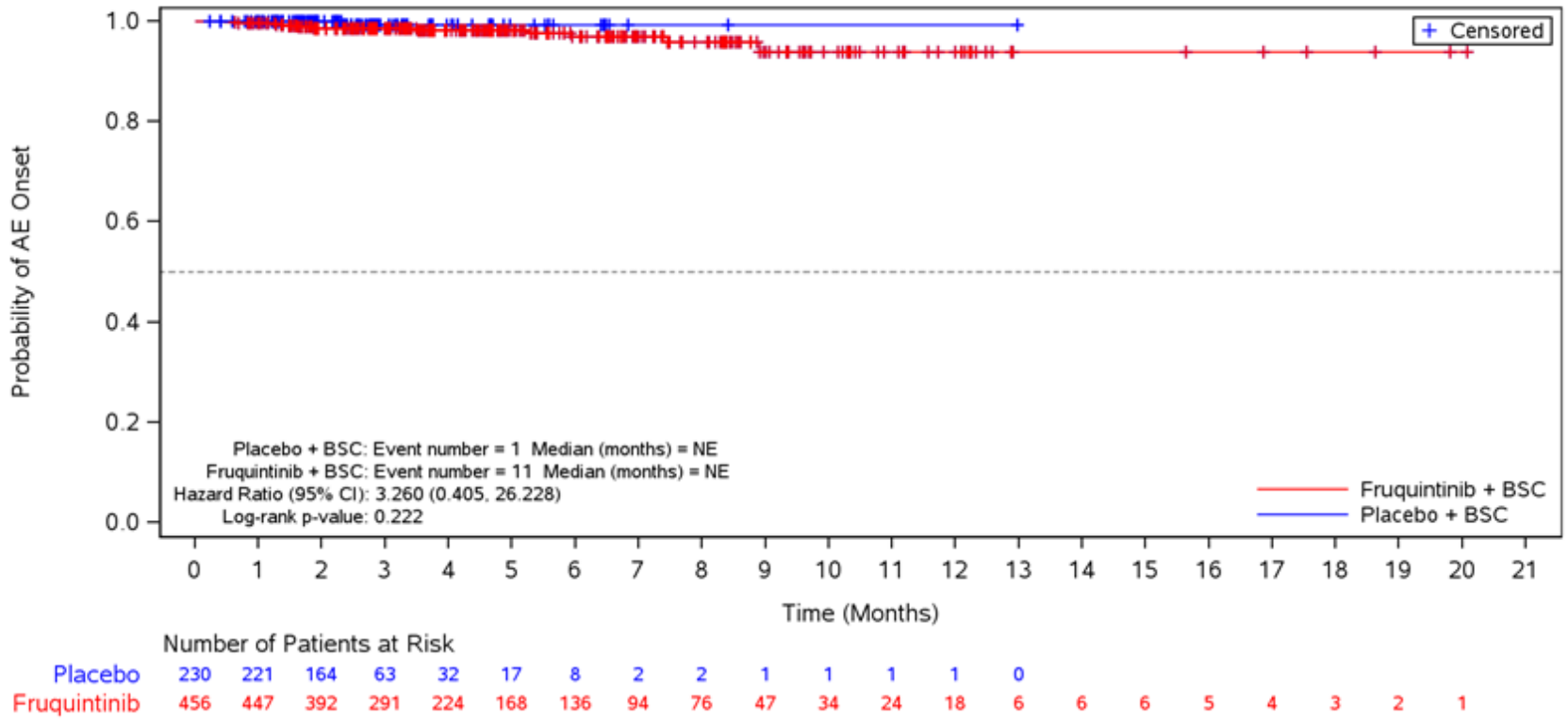
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE



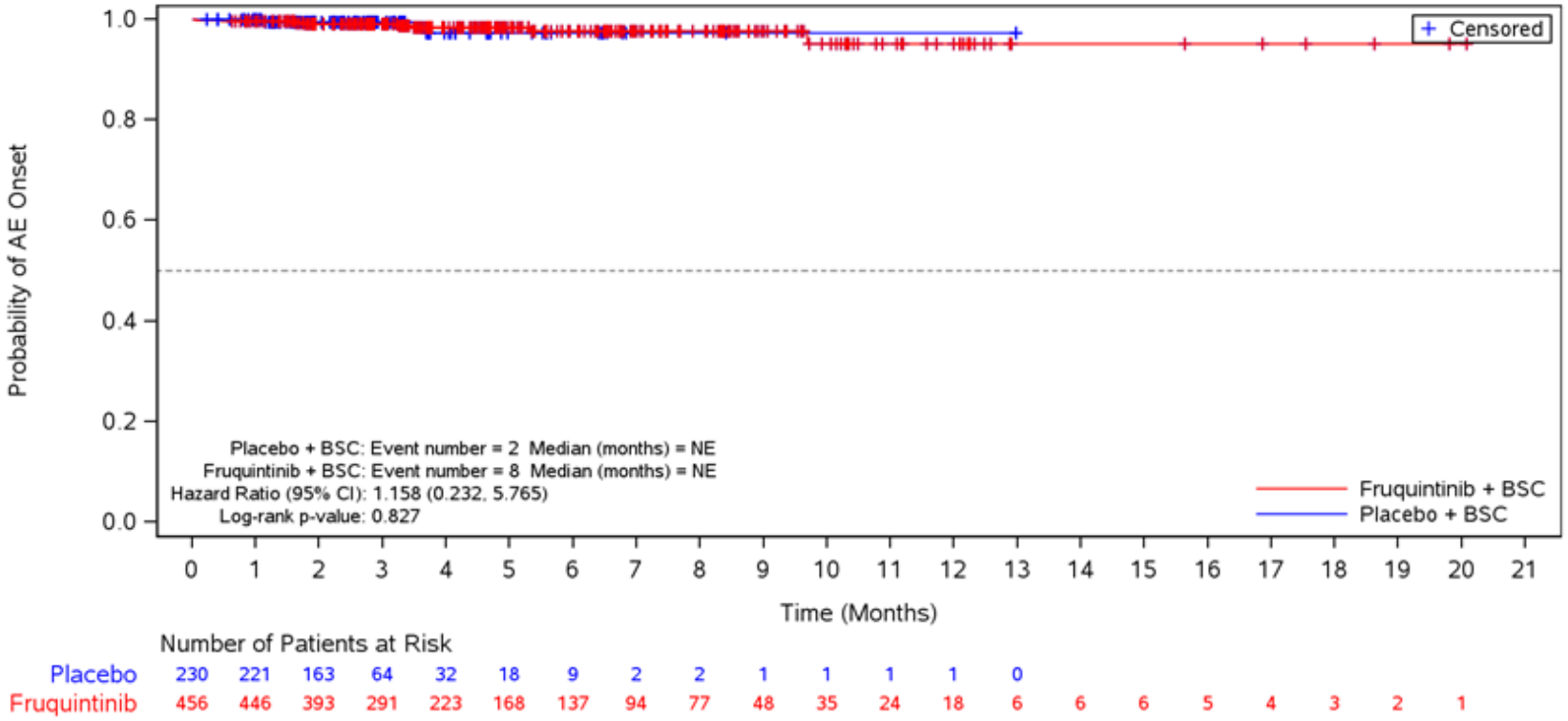
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE



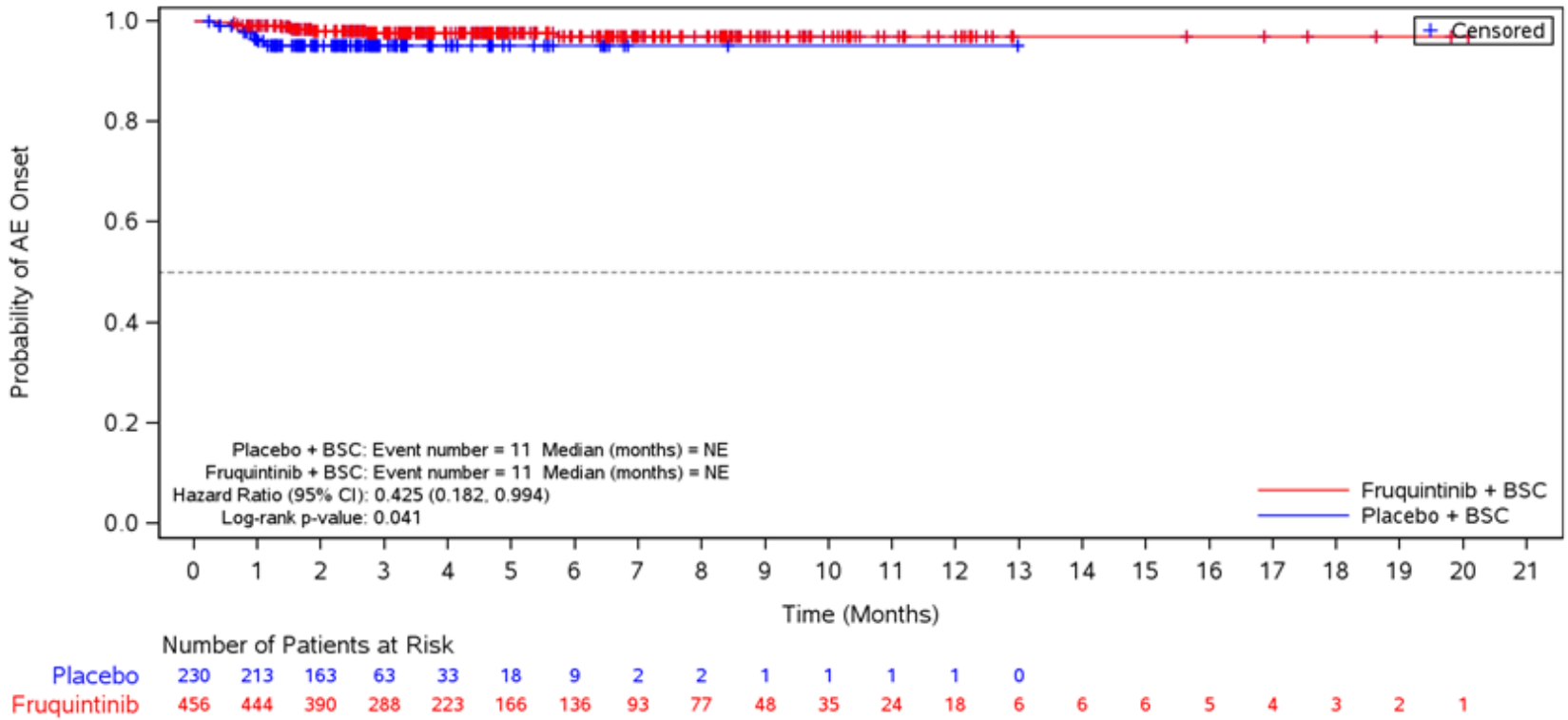
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE



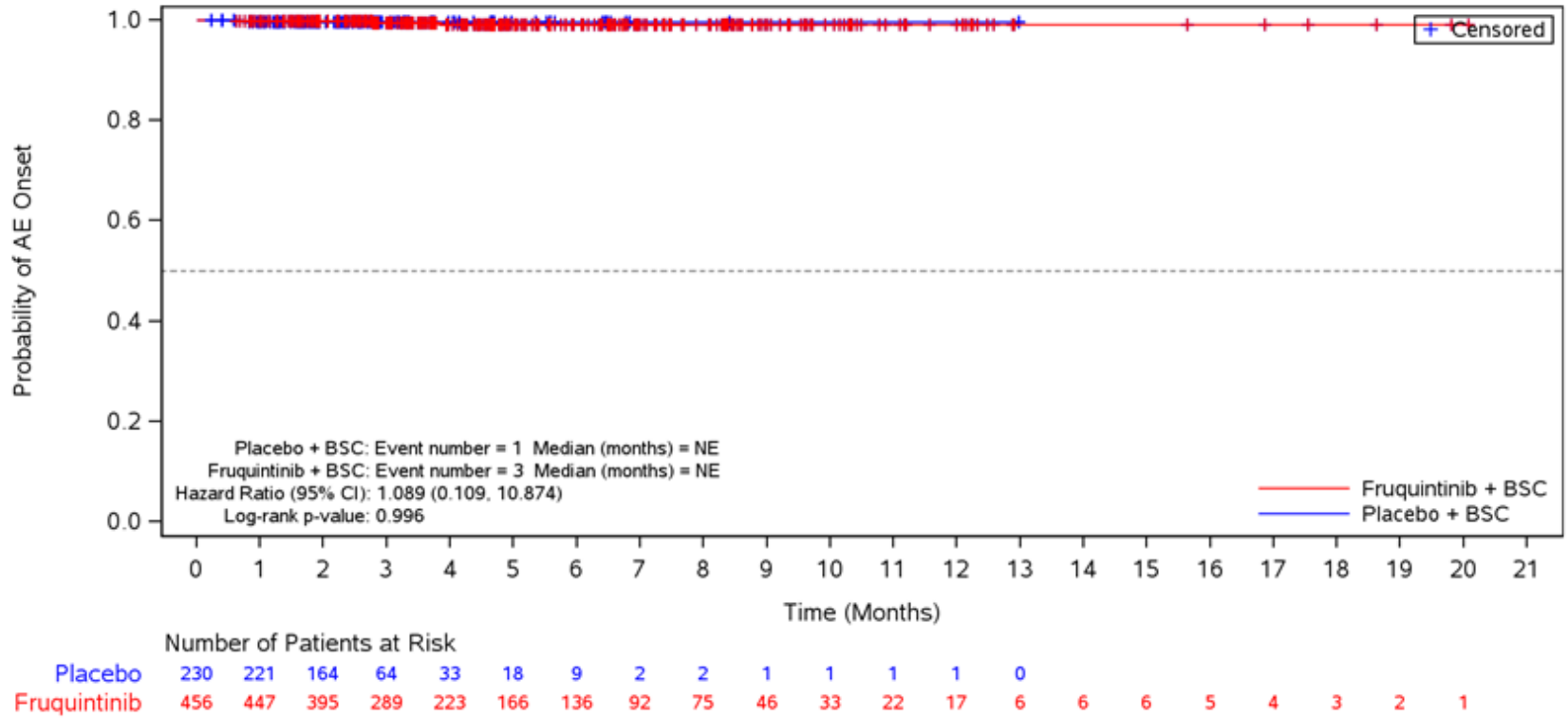
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE



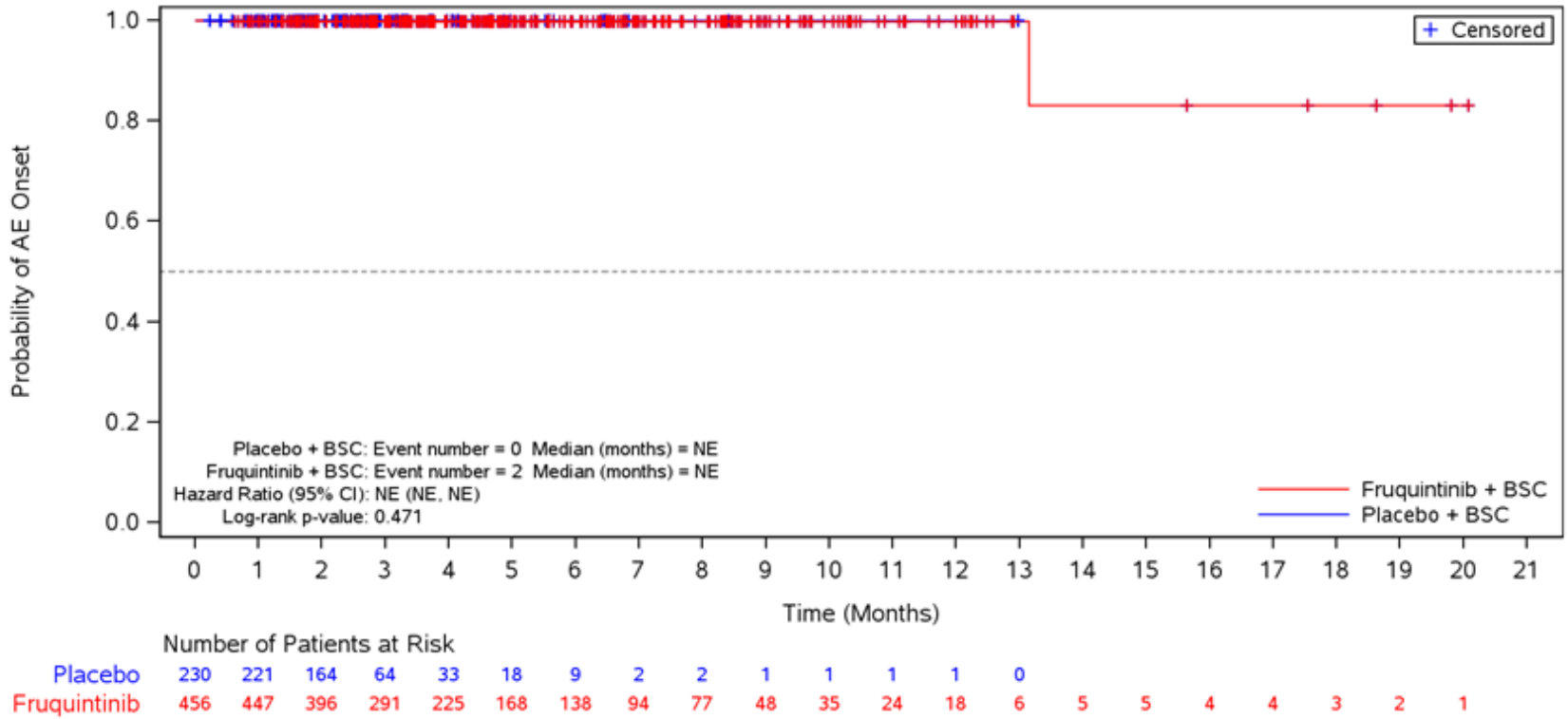
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE



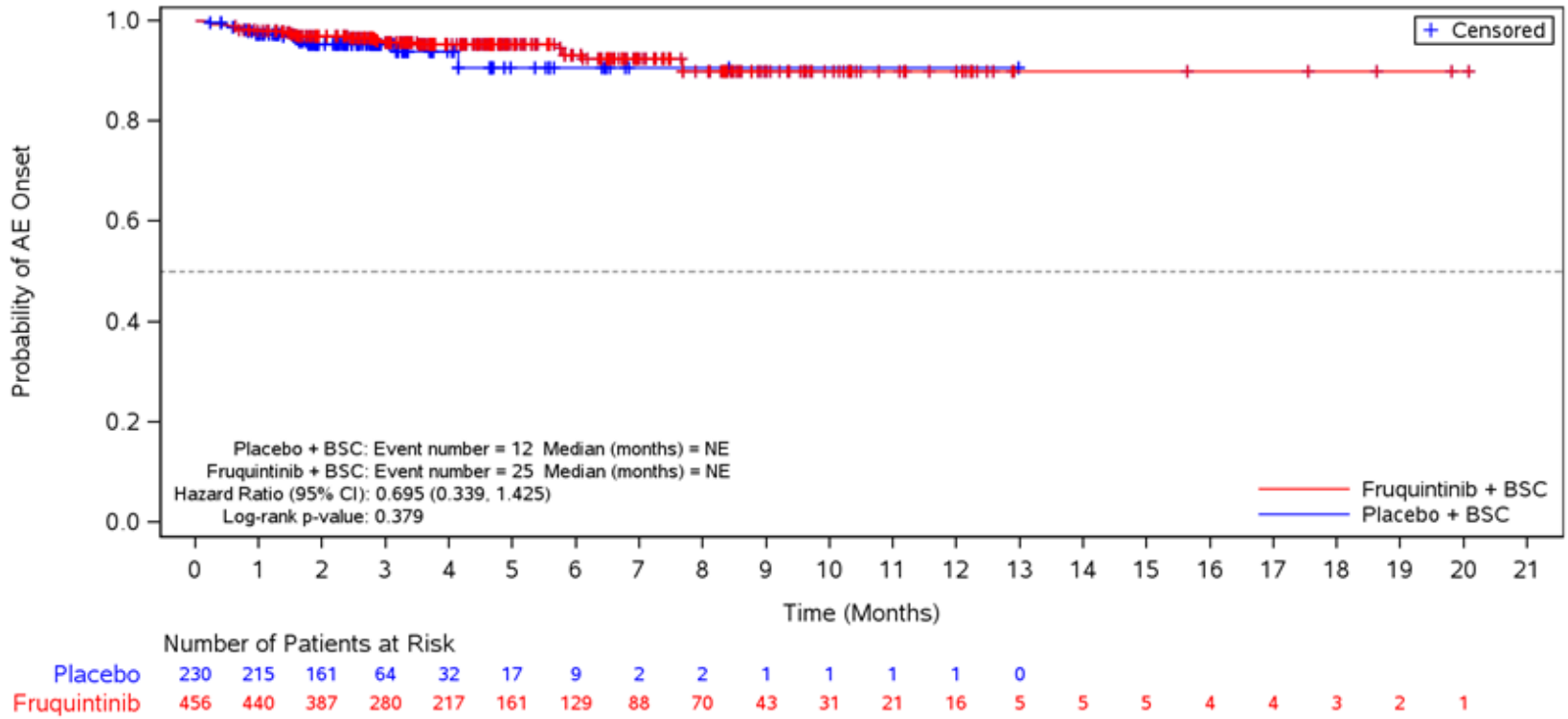
BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Figure 35.1.1.7.3.3A
Kaplan-Meier Plot for Time to Onset of TEAE of Infections
Safety Population
Serious TEAE



BSC=Best supportive care, TEAE=Treatment Emergent Adverse Event.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	1 (0.2)
Number of Subjects Censored, n (%)	230 (100.0)	455 (99.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.495

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
18 months	NE (NE, NE)	99.8 (99.3, 100.0)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Thyroid dysfunction
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	1 (0.2)
Number of Subjects Censored, n (%)	230 (100.0)	455 (99.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.523

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.3, 100.0)
18 months	NE (NE, NE)	99.8 (99.3, 100.0)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Proteinuria
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	8 (1.8)
Number of Subjects Censored, n (%)	230 (100.0)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.050

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
6 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
9 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
12 months	100.0 (100.0, 100.0)	98.2 (97.0, 99.4)
18 months	NE (NE, NE)	98.2 (97.0, 99.4)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hypertension
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	4 (1.7)	10 (2.2)
Number of Subjects Censored, n (%)	226 (98.3)	446 (97.8)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.6*, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.686 (0.615)
95% CI		(0.206, 2.286)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.598

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.1 (97.9, 100.0)	98.5 (97.3, 99.7)
6 months	93.5 (85.5, 100.0)	97.2 (95.3, 99.1)
9 months	93.5 (85.5, 100.0)	95.8 (92.6, 99.1)
12 months	93.5 (85.5, 100.0)	95.8 (92.6, 99.1)
18 months	NE (NE, NE)	95.8 (92.6, 99.1)

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Haemorrhages
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	11 (2.4)
Number of Subjects Censored, n (%)	229 (99.6)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		3.260 (1.064)
95% CI		(0.405, 26.228)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.222

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.4 (98.1, 100.0)	98.6 (97.6, 99.7)
6 months	99.4 (98.1, 100.0)	96.9 (94.7, 99.2)
9 months	99.4 (98.1, 100.0)	93.9 (89.1, 98.7)
12 months	99.4 (98.1, 100.0)	93.9 (89.1, 98.7)
18 months	NE (NE, NE)	93.9 (89.1, 98.7)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Gastrointestinal perforation
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	2 (0.9)	8 (1.8)
Number of Subjects Censored, n (%)	228 (99.1)	448 (98.2)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.158 (0.819)
95% CI		(0.232, 5.765)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.827

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.5 (98.6, 100.0)	99.1 (98.2, 100.0)
6 months	97.3 (93.0, 100.0)	97.7 (95.9, 99.5)
9 months	97.3 (93.0, 100.0)	97.7 (95.9, 99.5)
12 months	97.3 (93.0, 100.0)	95.2 (89.9, 100.0)
18 months	NE (NE, NE)	95.2 (89.9, 100.0)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Embolic and thrombotic events
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.86

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	11 (4.8)	11 (2.4)
Number of Subjects Censored, n (%)	219 (95.2)	445 (97.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.4, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.425 (0.433)
95% CI		(0.182, 0.994)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.041

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.1 (92.3, 97.9)	97.7 (96.3, 99.1)
6 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
9 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
12 months	95.1 (92.3, 97.9)	97.0 (95.1, 98.9)
18 months	NE (NE, NE)	97.0 (95.1, 98.9)

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Hepatic function abnormal
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.78

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	1 (0.4)	3 (0.7)
Number of Subjects Censored, n (%)	229 (99.6)	453 (99.3)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.5, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		1.089 (1.174)
95% CI		(0.109, 10.874)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.996

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	99.6 (98.7, 100.0)	99.5 (98.8, 100.0)
6 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
9 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
12 months	99.6 (98.7, 100.0)	99.1 (98.0, 100.0)
18 months	NE (NE, NE)	99.1 (98.0, 100.0)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Left ventricular ejection fraction decreased
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.88

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	0	2 (0.4)
Number of Subjects Censored, n (%)	230 (100.0)	454 (99.6)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (13.14, NE)
Median (95% CI)	NE (NE, NE)	NE (13.14, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.3, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		NE (NE)
95% CI		(NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.471

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
6 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
9 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
12 months	100.0 (100.0, 100.0)	99.8 (99.4, 100.0)
18 months	NE (NE, NE)	83.2 (53.4, 100.0)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Dermatological toxicity
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Median Follow-up Time (months)	2.83	3.94

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Number of Subjects with Events, n (%)	12 (5.2)	25 (5.5)
Number of Subjects Censored, n (%)	218 (94.8)	431 (94.5)
Time to first TEAE (months)		
25% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
75% percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.2*, 13.0*	0.1, 20.1*
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Hazard Ratio (SE)		0.695 (0.366)
95% CI		(0.339, 1.425)

* indicates censored value.
Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.
P-value is calculated using the stratified log-rank test.
Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Table 35.1.1.7.3.3A
Summary of Time to Onset of TEAE of Infections
Safety Population
Serious TEAE

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Log-rank p-value		0.379

* indicates censored value.

Note: The adjusted HR and its 95% CI are estimated using unstratified Cox's proportional hazards model in which the randomization schedule stratification factors and treatment group are covariates.

P-value is calculated using the stratified log-rank test.

Follow-up time (months) is calculated as ((last dose date + 37 days) – first dose date + 1)/30.4375.

Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; SE=Standard error.

Statistics	Placebo + BSC N=230	Fruquintinib + BSC N=456
Kaplan-Meier Estimates at % (95% CI)		
3 months	95.4 (92.6, 98.2)	95.7 (93.7, 97.7)
6 months	90.7 (83.5, 97.9)	93.2 (90.1, 96.3)
9 months	90.7 (83.5, 97.9)	90.0 (85.3, 94.7)
12 months	90.7 (83.5, 97.9)	90.0 (85.3, 94.7)
18 months	NE (NE, NE)	90.0 (85.3, 94.7)
Median Follow-up Time (months)	2.83	3.75

3. Endpunktspezifische Nachbeobachtungszeiten

Table 14.2.1.1.2
Overall Survival
(Intent-to-Treat Population)

Statistics	Placebo + BSC (N=230)	Fruquintinib + BSC (N=461)
Probability (%) of being alive at (95% CI)[c]		
3 months	68.8 (62.8, 74.9)	88.1 (85.1, 91.1)
6 months	41.5 (35.0, 48.0)	60.4 (55.9, 64.9)
9 months	28.2 (22.1, 34.3)	41.1 (36.4, 45.8)
12 months	23.2 (17.1, 29.2)	27.8 (23.0, 32.6)
18 months	10.3 (3.9, 16.8)	8.3 (2.3, 14.2)
Duration (Months) to follow-up [b],[d]		
25% percentile (95% CI)	8.7 (8.1, 9.6)	9.0 (8.5, 9.5)
Median (95% CI)	11.2 (9.9, 12.0)	11.3 (10.6, 12.4)
75% percentile (95% CI)	15.5 (12.1, 16.7)	14.2 (13.2, 15.4)
Min, Max	0.2*, 18.7	0.2, 18.9
Comparison (Fruquintinib + BSC vs Placebo + BSC)		
Stratified HR (SE) [e]		0.662 (0.096)
95% CI [e]		(0.549, 0.800)
Two-sided p-value [f]		<0.001

* indicates censored value.
[a] Percentage is based on the number of censored subjects.
[b] The median, 25% and 75% percentiles are calculated using the Kaplan-Meier method, and the corresponding 95% CIs are calculated from a log-log transformation based on the Brookmeyer-Crowley method.
[c] The survival probabilities and corresponding 95% CIs are calculated using a linear transformation based on the Brookmeyer-Crowley method at the selected landmarks.
[d] Duration (Months) to follow-up refers to the time interval between date of randomization and last date known to be alive for subjects who have not yet been reported to have died by the time of analysis. Subjects who were reported to have died would be censored at death date.
[e] The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors), in which treatment group is the only covariate in the model.
[f] P-value to test the treatment effect is calculated using the stratified log-rank test to account for the randomization schedule stratification factors.
Note: OS is defined as the time (months) from date of randomization to death from any cause and calculated as (date of death or last known alive - date of randomization + 1)/30.4375.
Note: Percentages are based on the number of subjects in each treatment group unless otherwise specified.
BSC=Best supportive care; CI=Confidence interval; HR=Hazard ratio; Max=Maximum; Min=Minimum; OS=Overall survival; SE=Standard error.
Source: Listing 16.2.6.2.2.

Table 35.1.2.1.2A
Summary of Progression Free Survival
Intent-to-Treat Population

Statistics	Placebo + BSC N=138	Fruquintinib + BSC N=278
Probability (%) of PFS (95% CI)		
1 month	83.7 (77.3, 90.1)	97.4 (95.5, 99.3)
3 months	11.3 (5.8, 16.9)	63.0 (57.2, 68.8)
6 months	2.4 (0.0, 5.1)	26.4 (21.0, 31.9)
9 months	1.6 (0.0, 3.8)	14.6 (10.1, 19.0)
12 months	NE (NE, NE)	7.7 (3.6, 11.7)
PFS Follow-up Time (month)	1.84	3.68
25% percentile (95% CI)	11.07 (NE, NE)	9.17 (7.36, 10.97)
Median (95% CI)	11.07 (NE, NE)	11.04 (9.33, 20.27)
75% percentile (95% CI)	11.07 (NE, NE)	20.27 (18.40, NE)
Min, Max	0.0, 11.1	0.0, 22.0

* indicates censored value.

[a] Only includes progression events that occur within 118 days of the last evaluable RECIST assessment. [b] RECIST progression event occurred > 118 days after last evaluable RECIST assessment (or date of randomisation in absence of evaluable baseline RECIST assessment). [c] Death occurred > 118 days after last evaluable RECIST assessment (or randomisation). [d] Subjects known to be alive without RECIST progression at data cut-off date. This excludes patients alive without evaluable baseline RECIST assessment or without evaluable on-study RECIST assessment. [e] Subjects censored at last evaluable RECIST assessment.

The median, 25% and 75% percentiles are calculated using the Kaplan-Meier method, and the corresponding 95% CIs are calculated from a linear transformation.

The survival probabilities and corresponding 95% CIs are calculated using a linear transformation.

The stratified HR and its 95% CI are estimated using stratified Cox's proportional hazards model (accounting for the randomization schedule stratification factors).

P-value is calculated using the unstratified log-rank test.

For subjects without tumor assessment at baseline or without any tumor assessment after baseline evaluation, they will be censored at the randomization date unless they die within 118 days from randomization. For subjects without death and tumor assessment after baseline evaluation, censoring date is the randomization date. If the subject progresses or dies after two or more consecutive missed tumor assessment visits, the subject will be censored at the time of the latest evaluable RECIST assessment. For subjects started new anti-cancer therapy prior to the documented disease progression or death on study, the subject will be censored at the time of the latest evaluable RECIST assessment.

Table 35.1.1.8.1A
Summary of Duration of Follow-Up (Months) for QoL Questionnaire
ITT Population

	Placebo + BSC N=230	Fruquintinib + BSC N=461
EQ-5D-5L VAS Score		
n	230	461
Mean (std dev)	1.80 (1.492)	3.85 (3.138)
Median	1.87	2.79
Min, Max	0.0, 11.6	0.0, 18.9
EORTC QLQ-C30 V3.0		
n	230	461
Mean (std dev)	1.76 (1.494)	3.83 (3.144)
Median	1.87	2.79
Min, Max	0.0, 11.6	0.0, 18.9

Duration of follow-up (months) is calculated as (last date of observed measurement - randomization date + 1)/30.4375.

Table 35.1.1.8.2A
Summary of Duration of Follow-Up for Safety
Safety Population

	Placebo + BSC N=230	Fruquintinib + BSC N=456
Safety follow-up to 30 days after last dose (month)		
n	230	456
Mean (std dev)	2.70 (1.425)	4.75 (3.139)
Median	2.60	3.71
Min, Max	0.2, 12.7	0.6, 19.8
Safety follow-up to 37 days after last dose (month)		
n	230	456
Mean (std dev)	2.88 (1.464)	4.95 (3.154)
Median	2.83	3.94
Min, Max	0.2, 13.0	0.6, 20.1