Clinical trial results:
A Phase 3, Multi-National, Double-Blind, Randomized, Placebo-Controlled, Stratified, Parallel Group, Study to Evaluate the Safety, Tolerability and Efficacy of Tirasemtiv in Patients with Amyotrophic Lateral Sclerosis (ALS)

Summary

EudraCT number	2014-005413-23
Trial protocol	DE GB IE NL ES PT BE IT
Global end of trial date	27 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

Trial information

Trial identification

Sponsor protocol code	CY4031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02496767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytokinetics, Inc.
Sponsor organisation address	280 East Grand Avenue, South San Francisco, United States, CA 94080
Public contact	Medical Affairs, Cytokinetics, Inc., +1 650 624 2929, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics, Inc., +1 650 624 2929, medicalaffairs@cytokinetics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2017
Global end of trial reached?	Yes
Global end of trial date	27 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of tirasemtiv versus placebo on respiratory function in patients with Amyotrophic Lateral Sclerosis (ALS).

Protection of trial subjects:

The study was conducted in accordance with International Council on Harmonisation (ICH) guidelines and local regulations in the applicable regions in which the study was conducted. Both the US regulations and the ICH guidelines are commonly known good clinical practices (GCP) and are consistent with the Declaration of Helsinki, 1996. Written informed consent was obtained with an IRB/EC/REB-approved ICF. A master ICF was developed by the sponsor; customized for each country by Parexel; further customized for the study center by the investigator (or designee); then approved by the sponsor. The ICF was then submitted by the investigator (or designee) to the IRB/EC/REB for approval. A copy of the IRB/EC/REB approved site-specific ICF was sent to the sponsor (or designee).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 424
Country: Number of subjects enrolled	Canada: 141
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Portugal: 4
Worldwide total number of subjects	744
EEA total number of subjects	179

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	541
From 65 to 84 years	202
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants who met all the inclusion and none of the exclusion criteria were enrolled at 79 sites in Belgium, Canada, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, the United Kingdom (UK), and the United States (US).

Pre-assignment

Screening details:

Participants attended a Screening Visit before receiving their first dose of tirasemtiv. All subjects underwent inclusion exclusion criteria assessment and all eligible subjects signed the informed consent before undergoing any study-related procedures.

Period 1

Period 1 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the open-label phase of the study, all patients received one tirasemtiv tablet (125 mg) twice daily for 14 days.

Number of subjects in period 1	Overall
Started	744
Completed	565
Not completed	179
Consent withdrawn by subject	1
Adverse Event	176
Protocol deviation	2

Period 2

Period 2 title	Double-Blind, Placebo-Controlled Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients randomized to the placebo group, received two tablets twice daily from Day 1 to end of Week 48. The matching placebo tablets contained excipients only.

Arm title	250 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients received one tirasemtiv tablet (125 mg) and one placebo tablet twice daily from Day 1 through Week 48.

Arm title	375 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients received one tirasemtiv tablet (125 mg) and one placebo tablet twice daily from Day 1 through Week 2. The target dose was escalated to 375 mg (one tirasemtiv tablet [125 mg] in the morning along with matching placebo and two tirasemtiv tables [250 mg] in the evening) from Week 3 through Week 48.

Arm title	500 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients received one tirasemtiv tablet (125 mg) and one placebo tablet twice daily from Day 1 through Week 2. The target dose was escalated to 375 mg [One tirasemtiv tablet (125 mg) in morning along with matching placebo and two tirasemtiv tablets (250 mg) in evening] on Weeks 3 and 4. The target dose was further escalated to 500 mg [Two tirasemtiv (250 mg) tablets in morning and two tirasemtiv tablets (250 mg) in evening] from Week 5 through Week 48.

Arm title	All (Tirasemtiv)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

This group includes all patients randomized to one of the 3 tirasemtiv dose groups (250 mg/day, 375 mg/day, or 500 mg/day). The patients received tirasemtiv from Week 1 through Week 48 in the double-blind, placebo-controlled phase.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is not the baseline period as it corresponds to the open-label, lead-in phase of the study. In order to capture the baseline characteristics for placebo and treatment groups (Tirasemtiv 250mg, 375mg and 500mg), period 2 (Double-Blind, Placebo-Controlled Phase) is selected as the baseline period.

Number of subjects in period 2	Placebo	250 mg	375 mg
Started	188	126	126
Completed	132	80	65
Not completed	56	46	61
Consent withdrawn by subject	4	3	1
Physician decision	4	1	-
Adverse Event	13	23	43
Death	10	6	2
Other	9	4	5
Progressive disease	13	9	8
Lost to follow-up	2	-	2
Protocol deviation	1	-	-

Number of subjects in period 2	500 mg	All (Tirasemtiv)
Started	125	377
Completed	59	204
Not completed	66	173
Consent withdrawn by subject	2	6
Physician decision	-	1
Adverse Event	43	109
Death	4	12
Other	2	11

Progressive disease	14	31
Lost to follow-up	1	3
Protocol deviation	-	-

Period 3	
Period 3 title	Withdrawal Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were maintained on placebo dose given during the double-blind, placebo-controlled phase from Week 49 through Week 52.

Arm title	Tirasemtiv/Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were withdrawn from the Tirasemtiv group and were given placebo from Week 49 through Week 52.

Arm title	Tirasemtiv/Tirasemtiv

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were maintained on tirasemtiv dose given during the double-blind, placebo-controlled

phase from Week 49 through Week 52.

Number of subjects in period 3	Placebo	Tirasemtiv/Placebo	Tirasemtiv/Tirasemtiv
Started	132	103	101
Completed	126	99	96
Not completed	6	4	5
Consent withdrawn by subject	1	1	1
Adverse Event	1	2	1
Death	-	1	2
Progressive disease	4	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	250 mg
Reporting group description: -	
Reporting group title	375 mg
Reporting group description: -	
Reporting group title	500 mg
Reporting group description: -	
Reporting group title	All (Tirasemtiv)
Reporting group description: -	

Reporting group values	Placebo	250 mg	375 mg
Number of subjects	188	126	126
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	55.9	57.1	57.3
standard deviation	± 10.63	± 10.20	± 9.06
Gender categorical Units: Subjects			
Female	65	30	42
Male	123	96	84

Reporting group values	500 mg	All (Tirasemtiv)	Total
Number of subjects	125	377	565
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 56.4 ± 10.94	 56.9 ± 10.08	 -
Gender categorical Units: Subjects			
Female	38	110	175
Male	87	267	390

End points

End points reporting groups

Reporting group title	Overall
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	250 mg
Reporting group description: -	
Reporting group title	375 mg
Reporting group description: -	
Reporting group title	500 mg
Reporting group description: -	
Reporting group title	All (Tirasemtiv)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Tirasemtiv/Placebo
Reporting group description: -	
Reporting group title	Tirasemtiv/Tirasemtiv
Reporting group description: -	

Primary: Change in percent predicted slow vital capacity (SVC) from baseline to week 24

End point title	Change in percent predicted slow vital capacity (SVC) from baseline to week 24

End point description:

Respiratory assessments consisted of SVC. SVC was measured with a spirometer. Patients were instructed to take 3 to 5 regular breaths, followed by as deep an inspiration as possible, followed by a slow and steady exhalation of as much air volume as possible. Patients were to perform at least 3 SVC tests at each designated visit. Up to 2 additional SVC tests could have been performed if the variability during the first 3 tests was >10%

End point type	Primary

End point timeframe:

Day 1 through Week 24

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Percentage (%)				
least squares mean (standard error)	-14.354 (± 1.2270)	-12.648 (± 1.5165)	-13.742 (± 1.6076)	-13.927 (± 1.7213)

End point values	All (Tirasemtiv)			

Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Percentage (%)				
least squares mean (standard error)	-13.439 (± 0.9615)			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3782 [1]
Method	Multiple imputation, mixed model ANCOVA
Parameter estimate	LS mean difference vs.placebo
Point estimate	1.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.089
upper limit	5.503
Variability estimate	Standard error of the mean
Dispersion value	1.9365

Notes:

[1] - Missing data were imputed using multiple imputation

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7625 [2]
Method	Multiple imputation, mixed model ANCOVA
Parameter estimate	LS mean difference vs.placebo
Point estimate	0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.359
upper limit	4.583
Variability estimate	Standard error of the mean
Dispersion value	2.0245

Notes:

[2] - Missing data were imputed using multiple imputation

Statistical analysis title	Tirasemtiv 500mg vs. Placebo
Comparison groups	Placebo v 500 mg

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8394 [3]
Method	Multiple imputation, mixed model ANCOVA
Parameter estimate	LS mean difference vs.placebo
Point estimate	0.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.711
upper limit	4.566
Variability estimate	Standard error of the mean
Dispersion value	2.1081

Notes:

[3] - Missing data were imputed using multiple imputation

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5552 [4]
Method	Multiple imputation, mixed model ANCOVA
Parameter estimate	LS mean difference vs.placebo
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.127
upper limit	3.958
Variability estimate	Standard error of the mean
Dispersion value	1.5513

Notes:

[4] - Missing data were imputed using multiple imputation

Secondary: Change in ALS Functional Rating Scale-Revised (ALSFRS-R) respiratory domain score from baseline to Week 48

End point title	Change in ALS Functional Rating Scale-Revised (ALSFRS-R) respiratory domain score from baseline to Week 48

End point description:

The ALSFRS-R consists of 12 questions, assessing a patient’s capability and independence in functional activities relevant to ALS, categorized in 4 domains: gross motor tasks, fine motor tasks, bulbar functions, and respiratory function. Each question was scored on a scale from 0 (indicating incapable or dependent) to 4 (normal).

End point type	Secondary

End point timeframe:

Week 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Units on scale				
least squares mean (standard error)	-2.26 (± 0.258)	-1.95 (± 0.320)	-2.41 (± 0.340)	-2.59 (± 0.355)

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Units on scale				
least squares mean (standard error)	-2.29 (± 0.195)			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4521
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.41

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.712
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	0.426

Statistical analysis title	Tirasemtiv 500mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.439

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.916
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.323

Secondary: Slope of mega-score of muscle strength over 48 Weeks	
End point title	Slope of mega-score of muscle strength over 48 Weeks

End point description:

Muscle strength as determined by the mega-score of:
• Elbow flexion (bilateral)
• Wrist extension (bilateral)
• Knee extension (bilateral)
• Ankle dorsiflexion (bilateral)
• Handgrip strength (bilateral)

End point type	Secondary

End point timeframe:

Week 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Slope				
number (confidence interval 95%)	-0.1501 (-0.1729 to -0.1272)	-0.1512 (-0.1794 to -0.1230)	-0.1434 (-0.1742 to -0.1126)	-0.1413 (-0.1730 to -0.1095)

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Slope				
number (confidence interval 95%)	-0.1454 (-0.1628 to -0.1279)			

Statistical analyses

Statistical analysis title	Difference in slope Tirasemtiv 250mg vs. placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9505
Method	Repeated measures mixed model
Parameter estimate	Slope
Point estimate	-0.0011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0374
upper limit	0.0351

Statistical analysis title	Difference in slope Tirasemtiv 375mg vs. placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7336
Method	Repeated measures mixed model
Parameter estimate	Slope
Point estimate	0.0066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0317
upper limit	0.045

Statistical analysis title	Difference in slope Tirasemtiv 500mg vs. placebo
Comparison groups	Placebo v 500 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6593
Method	Repeated measures mixed model
Parameter estimate	Slope
Point estimate	0.0088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0303
upper limit	0.0479

Statistical analysis title	Difference in slope All (Tirasemtiv) vs. placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7482
Method	Repeated measures mixed model
Parameter estimate	Slope
Point estimate	0.0047

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.0334

Secondary: Time to the first occurrence of a decline in percent predicted SVC ≥20 percentage points or the onset of respiratory insufficiency or death from baseline to Week 48

End point title	Time to the first occurrence of a decline in percent predicted SVC ≥20 percentage points or the onset of respiratory insufficiency or death from baseline to Week 48

End point description:

To assess the time to the first occurrence of a decline from baseline in percent predicted SVC ≥ 20 percentage points or the onset of respiratory insufficiency (defined as tracheostomy or the use of non-invasive ventilation for ≥ 22 hours per day for ≥10 consecutive days) or death during all 48 weeks of double-blind, placebo-controlled treatment phase.

End point type	Secondary

End point timeframe:

Day 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Units on scale				
number (not applicable)				
Death	0	0	1	0
Decline from baseline in percent predicted SVC	98	58	56	57
Non-invasive ventilation for >=22 hours per day	0	0	1	0

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Units on scale				
number (not applicable)				
Death	1			
Decline from baseline in percent predicted SVC	171			
Non-invasive ventilation for >=22 hours per day	1			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2369
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.818
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.587
upper limit	1.141

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.942
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.988
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.711
upper limit	1.372

Statistical analysis title	Tirasemtiv 500mg vs. Placebo
Comparison groups	Placebo v 500 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6853
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.933
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668
upper limit	1.304

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4642
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.707
upper limit	1.172

Secondary: Time to the first occurrence of SVC ≤50% predicted or the onset of respiratory insufficiency or death over 48 Weeks

End point title	Time to the first occurrence of SVC ≤50% predicted or the onset of respiratory insufficiency or death over 48 Weeks

End point description:

SVC was measured with a spirometer. Patients were instructed to take 3 to 5 regular breaths, followed by as deep an inspiration as possible, followed by a slow and steady exhalation of as much air volume as possible. Patients were to perform at least 3 SVC tests at each designated visit. Up to 2 additional SVC tests could have been performed if the variability during the first 3 tests was >10%. This endpoint assessed a decline in SVC to ≤ 50% predicted or the onset of respiratory insufficiency or death during all 48 weeks of double-blind, placebo-controlled treatment.

End point type	Secondary

End point timeframe:

Week 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Units on scale				
number (not applicable)				
Death	0	0	1	0
Decline in SVC to <=50% Predicted	54	39	27	32
Non-invasive ventilation for >=22 hours per day	3	0	1	0
Tracheostomy	0	0	1	0

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Units on scale				
number (not applicable)				
Death	1			
Decline in SVC to <=50% Predicted	98			
Non-invasive ventilation for >=22 hours per day	1			
Tracheostomy	1			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7667
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	1.627

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6619
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.904
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.577
upper limit	1.419

Statistical analysis title	Tirasemtiv 500mg vs. Placebo

Comparison groups	Placebo v 500 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5856
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.561
upper limit	1.386

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7563
Method	Repeated measures mixed model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.948
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	1.327

Secondary: Change in ALSFRS-R total score from baseline to Week 48

End point title	Change in ALSFRS-R total score from baseline to Week 48

End point description:

The ALSFRS-R consists of 12 questions, assessing a patient’s capability and independence in functional activities relevant to ALS, categorized in 4 domains: gross motor tasks, fine motor tasks, bulbar functions, and respiratory function. Each question was scored on a scale from 0 (indicating incapable or dependent) to 4 (normal). This endpoint assessed change from baseline in the ALSFRS-R total score to the end of 48 weeks of double-blind, placebo-controlled treatment.

End point type	Secondary

End point timeframe:

Week 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Units on scale				
least squares mean (standard error)	-11.39 (± 0.695)	-11.39 (± 0.859)	-12.19 (± 0.903)	-11.99 (± 0.937)

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Units on scale				
least squares mean (standard error)	-11.83 (± 0.519)			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9991
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	2.17
Variability estimate	Standard error of the mean
Dispersion value	1.103

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4808
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	1.138

Statistical analysis title	Tirasemtiv 500mg vs. Placebo
Comparison groups	Placebo v 500 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6082
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	1.69
Variability estimate	Standard error of the mean
Dispersion value	1.165

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6116
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	1.26

Secondary: Time to the first use of mechanical ventilatory assistance or death over 48 Weeks

End point title	Time to the first use of mechanical ventilatory assistance or death over 48 Weeks

End point description:

To assess the time to the first use of mechanical ventilatory assistance or death during all 48 weeks of double-blind, placebo-controlled treatment. Mechanical ventilatory assistance was defined as invasive or non-invasive ventilation for at least 2 hours over a 24-hour period for at least 5 consecutive days.

End point type	Secondary

End point timeframe:

Week 1 through Week 48

End point values	Placebo	250 mg	375 mg	500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	188	126	125	122
Units: Days				
number (not applicable)				
Death	11	3	5	4
Non-invasive ventilation for at least 2 hours	48	26	31	29
Tracheostomy	1	2	1	0

End point values	All (Tirasemtiv)			
Subject group type	Reporting group			
Number of subjects analysed	373			
Units: Days				
number (not applicable)				
Death	12			
Non-invasive ventilation for at least 2 hours	86			
Tracheostomy	3			

Statistical analyses

Statistical analysis title	Tirasemtiv 250mg vs. Placebo
Comparison groups	Placebo v 250 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2602
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.206

Statistical analysis title	Tirasemtiv 375mg vs. Placebo
Comparison groups	Placebo v 375 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6748
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.662

Statistical analysis title	Tirasemtiv 500mg vs. Placebo
Comparison groups	Placebo v 500 mg
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7694
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.938
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.609
upper limit	1.443

Statistical analysis title	All (Tirasemtiv) vs. Placebo
Comparison groups	Placebo v All (Tirasemtiv)
Number of subjects included in analysis	561
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6454
Method	Repeated measures mixed model
Parameter estimate	LS mean difference vs.placebo
Point estimate	0.926

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668
upper limit	1.284

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Week 2 (open-label phase) to Week 56 (follow-up visit)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	250 mg
Reporting group description: -	
Reporting group title	375 mg
Reporting group description: -	
Reporting group title	500 mg
Reporting group description: -	

Serious adverse events	Placebo	250 mg	375 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 188 (30.85%)	34 / 126 (26.98%)	37 / 126 (29.37%)
number of deaths (all causes)	11	7	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Genital neoplasm malignant female			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			

subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular cancer metastatic			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Device dislocation			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Euthanasia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Sudden death			
subjects affected / exposed	2 / 188 (1.06%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	1 / 1	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial secretion retention			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			

subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased bronchial secretion			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	4 / 188 (2.13%)	0 / 126 (0.00%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Pulmonary embolism			
subjects affected / exposed	3 / 188 (1.60%)	3 / 126 (2.38%)	4 / 126 (3.17%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory depression			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	11 / 188 (5.85%)	6 / 126 (4.76%)	7 / 126 (5.56%)
occurrences causally related to treatment / all	0 / 11	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 6	0 / 8	0 / 4
Sleep apnoea syndrome			
subjects affected / exposed	2 / 188 (1.06%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with anxiety			

subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			

subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary function test decreased			
subjects affected / exposed	3 / 188 (1.60%)	1 / 126 (0.79%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	2 / 188 (1.06%)	5 / 126 (3.97%)	4 / 126 (3.17%)
occurrences causally related to treatment / all	0 / 2	1 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic arthritis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			

subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	4 / 188 (2.13%)	2 / 126 (1.59%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cor pulmonale acute			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	2 / 188 (1.06%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	5 / 188 (2.66%)	2 / 126 (1.59%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 2
Basal ganglia stroke			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clonus			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasticity			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	9 / 188 (4.79%)	13 / 126 (10.32%)	10 / 126 (7.94%)
occurrences causally related to treatment / all	0 / 9	0 / 13	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	1 / 188 (0.53%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis interstitial			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain in extremity			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 188 (1.06%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	2 / 188 (1.06%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			

subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 188 (2.13%)	1 / 126 (0.79%)	4 / 126 (3.17%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia bacteraemia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 188 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 188 (0.00%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	500 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 125 (28.80%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Genital neoplasm malignant female			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma metastatic				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Testicular cancer metastatic				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Device malfunction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Euthanasia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial secretion retention				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoventilation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Increased bronchial secretion				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory depression				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	6 / 125 (4.80%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 5			
Sleep apnoea syndrome				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Adjustment disorder with anxiety				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucination, auditory				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination, visual				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abnormal behaviour				

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test decreased			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Traumatic arthritis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic haematoma				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Traumatic fracture				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arteriosclerosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cor pulmonale acute				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amyotrophic lateral sclerosis				
subjects affected / exposed	4 / 125 (3.20%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Basal ganglia stroke				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebellar infarction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular insufficiency				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clonus				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle spasticity				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thalamic infarction				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxic encephalopathy				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain upper				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal polyp				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal spasm			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis interstitial			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis bacterial			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Klebsiella bacteraemia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Otitis externa			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media acute			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Serratia bacteraemia			

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	250 mg	375 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 188 (98.40%)	126 / 126 (100.00%)	125 / 126 (99.21%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 188 (5.32%)	5 / 126 (3.97%)	5 / 126 (3.97%)
occurrences (all)	10	7	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 188 (13.83%)	15 / 126 (11.90%)	22 / 126 (17.46%)
occurrences (all)	35	19	26
Fatigue			
subjects affected / exposed	74 / 188 (39.36%)	47 / 126 (37.30%)	59 / 126 (46.83%)
occurrences (all)	94	73	88
Gait disturbance			
subjects affected / exposed	18 / 188 (9.57%)	13 / 126 (10.32%)	10 / 126 (7.94%)
occurrences (all)	21	17	12
Oedema peripheral			
subjects affected / exposed	21 / 188 (11.17%)	11 / 126 (8.73%)	8 / 126 (6.35%)
occurrences (all)	31	12	8
Peripheral swelling			
subjects affected / exposed	9 / 188 (4.79%)	9 / 126 (7.14%)	0 / 126 (0.00%)
occurrences (all)	10	11	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 188 (14.89%)	13 / 126 (10.32%)	17 / 126 (13.49%)
occurrences (all)	37	16	27
Dyspnoea			
subjects affected / exposed	41 / 188 (21.81%)	17 / 126 (13.49%)	24 / 126 (19.05%)
occurrences (all)	58	21	33
Nasal congestion			
subjects affected / exposed	15 / 188 (7.98%)	12 / 126 (9.52%)	12 / 126 (9.52%)
occurrences (all)	15	12	12
Psychiatric disorders			

Anxiety			
subjects affected / exposed	26 / 188 (13.83%)	18 / 126 (14.29%)	14 / 126 (11.11%)
occurrences (all)	29	21	17
Confusional state			
subjects affected / exposed	3 / 188 (1.60%)	3 / 126 (2.38%)	6 / 126 (4.76%)
occurrences (all)	4	4	6
Depression			
subjects affected / exposed	23 / 188 (12.23%)	9 / 126 (7.14%)	25 / 126 (19.84%)
occurrences (all)	27	12	26
Euphoric mood			
subjects affected / exposed	3 / 188 (1.60%)	8 / 126 (6.35%)	1 / 126 (0.79%)
occurrences (all)	3	9	1
Insomnia			
subjects affected / exposed	27 / 188 (14.36%)	25 / 126 (19.84%)	25 / 126 (19.84%)
occurrences (all)	33	31	30
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 188 (1.60%)	3 / 126 (2.38%)	2 / 126 (1.59%)
occurrences (all)	3	3	2
Weight decreased			
subjects affected / exposed	41 / 188 (21.81%)	41 / 126 (32.54%)	44 / 126 (34.92%)
occurrences (all)	51	50	55
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	36 / 188 (19.15%)	16 / 126 (12.70%)	24 / 126 (19.05%)
occurrences (all)	58	33	34
Head injury			
subjects affected / exposed	6 / 188 (3.19%)	8 / 126 (6.35%)	3 / 126 (2.38%)
occurrences (all)	6	11	4
Laceration			
subjects affected / exposed	17 / 188 (9.04%)	8 / 126 (6.35%)	14 / 126 (11.11%)
occurrences (all)	22	13	18
Ligament sprain			
subjects affected / exposed	12 / 188 (6.38%)	6 / 126 (4.76%)	4 / 126 (3.17%)
occurrences (all)	16	8	6
Post-traumatic pain			

subjects affected / exposed	28 / 188 (14.89%)	17 / 126 (13.49%)	17 / 126 (13.49%)
occurrences (all)	58	33	29
Skin abrasion			
subjects affected / exposed	25 / 188 (13.30%)	22 / 126 (17.46%)	10 / 126 (7.94%)
occurrences (all)	51	39	13
Nervous system disorders			
Balance disorder			
subjects affected / exposed	5 / 188 (2.66%)	5 / 126 (3.97%)	4 / 126 (3.17%)
occurrences (all)	6	7	6
Dizziness			
subjects affected / exposed	101 / 188 (53.72%)	67 / 126 (53.17%)	67 / 126 (53.17%)
occurrences (all)	143	101	108
Dysarthria			
subjects affected / exposed	19 / 188 (10.11%)	15 / 126 (11.90%)	9 / 126 (7.14%)
occurrences (all)	24	23	12
Headache			
subjects affected / exposed	30 / 188 (15.96%)	17 / 126 (13.49%)	26 / 126 (20.63%)
occurrences (all)	49	32	34
Muscle contractions involuntary			
subjects affected / exposed	11 / 188 (5.85%)	16 / 126 (12.70%)	8 / 126 (6.35%)
occurrences (all)	19	18	11
Muscle spasticity			
subjects affected / exposed	4 / 188 (2.13%)	6 / 126 (4.76%)	11 / 126 (8.73%)
occurrences (all)	4	6	13
Paraesthesia			
subjects affected / exposed	3 / 188 (1.60%)	4 / 126 (3.17%)	2 / 126 (1.59%)
occurrences (all)	5	5	3
Somnolence			
subjects affected / exposed	23 / 188 (12.23%)	21 / 126 (16.67%)	22 / 126 (17.46%)
occurrences (all)	30	32	37
Tremor			
subjects affected / exposed	6 / 188 (3.19%)	7 / 126 (5.56%)	13 / 126 (10.32%)
occurrences (all)	7	7	14
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	10 / 188 (5.32%)	9 / 126 (7.14%)	1 / 126 (0.79%)
occurrences (all)	13	14	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 188 (2.13%)	4 / 126 (3.17%)	1 / 126 (0.79%)
occurrences (all)	4	4	1
Constipation			
subjects affected / exposed	46 / 188 (24.47%)	27 / 126 (21.43%)	21 / 126 (16.67%)
occurrences (all)	59	36	29
Diarrhoea			
subjects affected / exposed	24 / 188 (12.77%)	14 / 126 (11.11%)	11 / 126 (8.73%)
occurrences (all)	30	17	15
Dry mouth			
subjects affected / exposed	14 / 188 (7.45%)	11 / 126 (8.73%)	9 / 126 (7.14%)
occurrences (all)	14	12	9
Dyspepsia			
subjects affected / exposed	11 / 188 (5.85%)	5 / 126 (3.97%)	5 / 126 (3.97%)
occurrences (all)	11	8	6
Dysphagia			
subjects affected / exposed	35 / 188 (18.62%)	26 / 126 (20.63%)	24 / 126 (19.05%)
occurrences (all)	43	34	31
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 188 (4.26%)	6 / 126 (4.76%)	7 / 126 (5.56%)
occurrences (all)	11	7	7
Nausea			
subjects affected / exposed	51 / 188 (27.13%)	25 / 126 (19.84%)	41 / 126 (32.54%)
occurrences (all)	73	33	52
Salivary hypersecretion			
subjects affected / exposed	20 / 188 (10.64%)	15 / 126 (11.90%)	9 / 126 (7.14%)
occurrences (all)	25	19	10
Vomiting			
subjects affected / exposed	7 / 188 (3.72%)	5 / 126 (3.97%)	5 / 126 (3.97%)
occurrences (all)	13	5	9
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	9 / 188 (4.79%)	5 / 126 (3.97%)	4 / 126 (3.17%)
occurrences (all)	13	5	4
Rash			
subjects affected / exposed	12 / 188 (6.38%)	14 / 126 (11.11%)	3 / 126 (2.38%)
occurrences (all)	15	21	3
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	7 / 188 (3.72%)	9 / 126 (7.14%)	6 / 126 (4.76%)
occurrences (all)	8	10	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 188 (9.04%)	6 / 126 (4.76%)	7 / 126 (5.56%)
occurrences (all)	20	6	10
Back pain			
subjects affected / exposed	20 / 188 (10.64%)	11 / 126 (8.73%)	10 / 126 (7.94%)
occurrences (all)	25	15	13
Muscle spasms			
subjects affected / exposed	38 / 188 (20.21%)	24 / 126 (19.05%)	24 / 126 (19.05%)
occurrences (all)	48	30	31
Muscular weakness			
subjects affected / exposed	67 / 188 (35.64%)	54 / 126 (42.86%)	46 / 126 (36.51%)
occurrences (all)	128	105	89
Musculoskeletal pain			
subjects affected / exposed	25 / 188 (13.30%)	10 / 126 (7.94%)	10 / 126 (7.94%)
occurrences (all)	31	11	11
Musculoskeletal stiffness			
subjects affected / exposed	8 / 188 (4.26%)	8 / 126 (6.35%)	3 / 126 (2.38%)
occurrences (all)	9	8	6
Myalgia			
subjects affected / exposed	14 / 188 (7.45%)	6 / 126 (4.76%)	4 / 126 (3.17%)
occurrences (all)	16	8	4
Neck pain			
subjects affected / exposed	11 / 188 (5.85%)	4 / 126 (3.17%)	4 / 126 (3.17%)
occurrences (all)	14	5	6
Pain in extremity			

subjects affected / exposed	21 / 188 (11.17%)	9 / 126 (7.14%)	13 / 126 (10.32%)
occurrences (all)	26	18	17
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	35 / 188 (18.62%)	23 / 126 (18.25%)	20 / 126 (15.87%)
occurrences (all)	46	28	25
Upper respiratory tract infection			
subjects affected / exposed	17 / 188 (9.04%)	3 / 126 (2.38%)	4 / 126 (3.17%)
occurrences (all)	20	3	7
Urinary tract infection			
subjects affected / exposed	2 / 188 (1.06%)	5 / 126 (3.97%)	7 / 126 (5.56%)
occurrences (all)	2	7	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 188 (11.70%)	18 / 126 (14.29%)	19 / 126 (15.08%)
occurrences (all)	26	18	19

Non-serious adverse events	500 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 125 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 125 (4.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 125 (17.60%)		
occurrences (all)	23		
Fatigue			
subjects affected / exposed	57 / 125 (45.60%)		
occurrences (all)	83		
Gait disturbance			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	10		
Oedema peripheral			

subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	12		
Peripheral swelling			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	19 / 125 (15.20%)		
occurrences (all)	28		
Nasal congestion			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	9		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	26 / 125 (20.80%)		
occurrences (all)	34		
Confusional state			
subjects affected / exposed	6 / 125 (4.80%)		
occurrences (all)	9		
Depression			
subjects affected / exposed	23 / 125 (18.40%)		
occurrences (all)	23		
Euphoric mood			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	31 / 125 (24.80%)		
occurrences (all)	33		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	8		
Weight decreased			

subjects affected / exposed	33 / 125 (26.40%)		
occurrences (all)	38		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	18 / 125 (14.40%)		
occurrences (all)	27		
Head injury			
subjects affected / exposed	4 / 125 (3.20%)		
occurrences (all)	5		
Laceration			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	14		
Ligament sprain			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Post-traumatic pain			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	17		
Skin abrasion			
subjects affected / exposed	13 / 125 (10.40%)		
occurrences (all)	25		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	6 / 125 (4.80%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	73 / 125 (58.40%)		
occurrences (all)	110		
Dysarthria			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	16		
Headache			
subjects affected / exposed	24 / 125 (19.20%)		
occurrences (all)	32		
Muscle contractions involuntary			

subjects affected / exposed	13 / 125 (10.40%)		
occurrences (all)	14		
Muscle spasticity			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	10		
Paraesthesia			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	11		
Somnolence			
subjects affected / exposed	27 / 125 (21.60%)		
occurrences (all)	33		
Tremor			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	16		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	29 / 125 (23.20%)		
occurrences (all)	34		
Diarrhoea			
subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	10		
Dry mouth			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	7		
Dysphagia			

subjects affected / exposed occurrences (all)	14 / 125 (11.20%) 20		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	6 / 125 (4.80%) 8		
Nausea subjects affected / exposed occurrences (all)	33 / 125 (26.40%) 53		
Salivary hypersecretion subjects affected / exposed occurrences (all)	3 / 125 (2.40%) 5		
Vomiting subjects affected / exposed occurrences (all)	7 / 125 (5.60%) 11		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	7 / 125 (5.60%) 7		
Rash subjects affected / exposed occurrences (all)	9 / 125 (7.20%) 9		
Renal and urinary disorders			
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 125 (6.40%) 10		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 125 (3.20%) 4		
Back pain subjects affected / exposed occurrences (all)	10 / 125 (8.00%) 11		
Muscle spasms subjects affected / exposed occurrences (all)	19 / 125 (15.20%) 26		
Muscular weakness			

subjects affected / exposed	39 / 125 (31.20%)		
occurrences (all)	59		
Musculoskeletal pain			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	9		
Musculoskeletal stiffness			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	12		
Myalgia			
subjects affected / exposed	6 / 125 (4.80%)		
occurrences (all)	6		
Neck pain			
subjects affected / exposed	4 / 125 (3.20%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	11 / 125 (8.80%)		
occurrences (all)	16		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 125 (11.20%)		
occurrences (all)	19		
Upper respiratory tract infection			
subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	13		
Urinary tract infection			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 125 (18.40%)		
occurrences (all)	28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2015	• Allowed patients who did not tolerate a dose level of tirasemtiv to return to a previously tolerated dose (rather than the last tolerated dose) (Note: During the conduct of the study, patients were only returned the 250-mg/day dose.) • Ensured that the language regarding patients who were not taking riluzole was consistently worded and clarified throughout the protocol • Clarified that the investigator was to be alerted if the patient had lost ≥ 5% of body weight since baseline (Week −2 visit) prior to drug administration rather than if the patient had lost ≥ 5% of body weight since the screening visit
16 January 2016	• Increased the number of randomized patients from approximately 360 to approximately 477 (to power the primary endpoint at 90% rather than 80%) • Revised the order of the secondary endpoints that were to be tested in a hierarchal closed testing procedure • Reclassified the secondary endpoints outside the closed testing procedure as tertiary endpoints • Removed language regarding the interim analysis of the primary endpoint (evaluated after 24 weeks of double-blind treatment) prior to completion of the study (with the last patient out at 56 weeks) • Provided clarification and details regarding acceptable contraception for male participants and female participants of childbearing potential • Clarified the blinded safety monitoring procedures
26 June 2017	• Revised and redefined the order of testing for the secondary endpoints • Clarified that the methodology for the closed testing procedure for the primary and secondary efficacy endpoints was fully described in the SAP • Clarified the subgroup efficacy, PK, and pharmacodynamic analyses to align with the SAP • Clarified that patients who were randomized and discontinued from the study were to be encouraged to attend the remaining study visits and complete the associated assessments • Added an additional sponsor’s medical monitor

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported