Clinical trial results:
Phase II/III, Multicenter, Randomized, Parallel Group, Double-Blind, Placebo Controlled Study to Assess Safety and Efficacy of TRO19622 in Amyotrophic Lateral Sclerosis (ALS) Patients Treated with Riluzole

Summary

EudraCT number	2008-007320-25
Trial protocol	DE FR GB BE ES
Global end of trial date	15 September 2011

Results information

Result version number	v1 (current)
This version publication date	02 April 2017
First version publication date	02 April 2017

Trial information

Trial identification

Sponsor protocol code	WN29853

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00868166
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +4161 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +4161 6878333, global.trial_information@roche.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	02 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of TRO19622 330 milligrams (mg) once daily as add-on therapy to riluzole 50 mg twice daily in the treatment of participants suffering from ALS as compared to placebo, assessed by the overall survival at 18 months.

Protection of trial subjects:

This protocol complied with the principal laid down by the 18th World Medical Assembly (Helsinki, 1964 an following amendments) and all applicable amendments laid down by the World Medical Assemblies, as well as the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The trial complied with the laws and regulations of the country in which the study was performed, and any applicable guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2009
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	France: 221
Country: Number of subjects enrolled	Germany: 147
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Belgium: 25
Worldwide total number of subjects	512
EEA total number of subjects	512

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)	378
From 65 to 84 years	134
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 617 participants were screened, of which, 512 participants were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to TRO19622 once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.

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

Dosage and administration details:

Placebo matched to TRO19622 was administered once daily orally for 18 months.

Arm title	TRO19622

Arm description:

Participants received TRO19622 at a dose of 330 mg once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.

Arm type	Experimental
Investigational medicinal product name	TRO19622
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

TRO19622 was administered at a dose of 330 mg once daily orally for 18 months.

Number of subjects in period 1	Placebo	TRO19622
Started	253	259
Completed	139	147
Not completed	114	112
Consent withdrawn by subject	25	33
Death	65	58
Major protocol deviation	-	1
Adverse event	10	9
Non-compliance with study drug	1	1
Unspecified	10	9
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TRO19622 once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	
Reporting group title	TRO19622
Reporting group description:	
Participants received TRO19622 at a dose of 330 mg once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	

Reporting group values	Placebo	TRO19622	Total
Number of subjects	253	259	512
Age Categorical Units: Subjects			
<=18 years	0	0	0
>18 and <65 years	193	185	378
>=65 years	60	74	134
Age Continuous Units: years			
arithmetic mean	55.7	57.3	
standard deviation	± 11.2	± 11.2	-
Gender Categorical Units: Subjects			
Female	89	92	181
Male	164	167	331

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TRO19622 once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	
Reporting group title	TRO19622
Reporting group description:	
Participants received TRO19622 at a dose of 330 mg once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]
End point description:	
OS was calculated as the time from the date of randomization until the date of death or last follow-up at 18 months (or 548 days). Kaplan-Meier estimate was used for analysis. Intent-to-treat (ITT) population included all randomized participants irrespective of whether study medication was administered, and regardless of eligibility status. Here, '99999' represents data were not estimable as median value had not been reached in either of the treatment arms at 18 months.	
End point type	Primary
End point timeframe:	
Baseline until death due to any cause (up to Month 18)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: "No statistical analysis was planned for this endpoint."

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Were Alive

End point title	Percentage of Participants Who Were Alive
End point description:	
ITT population.	
End point type	Primary
End point timeframe:	
Baseline until death due to any cause (up to Month 18)	

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: percentage of participants				
number (confidence interval 95%)	67.5 (61 to 73.1)	69.4 (63 to 74.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71 [2]
Method	Logrank

Notes:

[2] - Stratified Log-Rank test. Stratification criteria: site of onset (bulbar or spinal)

Secondary: Time to Failure

End point title	Time to Failure

End point description:

Time to failure was defined as the time from randomization to the time of the occurrence at least one of the following 3 events: death, tracheostomy, or non-invasive ventilation. Non-invasive ventilation was defined as more than (>) 23 hours of non-invasive ventilation daily for 14 consecutive days. Kaplan-Meier estimate was used for analysis. ITT population. Here, '99999' represents data were not estimable as median value had not been reached in either of the treatment arms at 18 months.

End point type	Secondary

End point timeframe:

Baseline up to death, tracheostomy, or non-invasive ventilation, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Failure

End point title	Percentage of Participants With Failure

End point description:

Failure was defined as the occurrence at least one of the following 3 events: death, tracheostomy, or non-invasive ventilation. Non-invasive ventilation was defined as more than (>) 23 hours of non-invasive ventilation daily for 14 consecutive days. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to death, tracheostomy, or non-invasive ventilation, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: percentage of participants				
number (confidence interval 95%)	65.5 (59.1 to 71.2)	67.1 (60.5 to 72.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73 [3]
Method	Logrank

Notes:

[3] - Non-stratified Log-Rank test

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [4]
Method	Logrank

Notes:

[4] - Stratified Log-Rank test. Stratification criteria: site of onset (bulbar or spinal)

Secondary: Time to Total Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALS FRS-R) Global Score Less than (<) 30 or Death

End point title	Time to Total Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALS FRS-R) Global Score Less than (<) 30 or

	Death

End point description:

ALS FRS-R scale is a validated rating instrument for monitoring the progression of disability in ALS participants. Participants were asked to rate their functions for the following 12 parameters each on the scale of 0-4 (higher score indicated normal function): speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, respiratory insufficiency. Global score was the sum of individual scores and ranged from 0-48 (higher score indicated normal function). Time to ALS FRS-R global score <30 or death was reported. Kaplan-Meier estimate was used for analysis. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to ALS FRS-R global score <30 or death, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: days				
median (confidence interval 95%)	341 (265 to 358)	372 (336 to 448)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without ALS FRS-R Global Score <30 or Death

End point title	Percentage of Participants Without ALS FRS-R Global Score <30 or Death

End point description:

ALS FRS-R scale is a validated rating instrument for monitoring the progression of disability in ALS participants. Participants were asked to rate their functions for the following 12 parameters each on the scale of 0-4 (higher score indicated normal function): speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, respiratory insufficiency. Global score was the sum of individual scores and ranged from 0-48 (higher score indicated normal function). Percentage of participants without ALS FRS-R global score <30 or death was reported. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to ALS FRS-R global score <30 or death, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: percentage of participants				
number (confidence interval 95%)	24.9 (19.2 to 30.8)	28.2 (22.5 to 34.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [5]
Method	Logrank

Notes:

[5] - Stratified Log-Rank test. Stratification criteria: site of onset (bulbar or spinal)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [6]
Method	Logrank

Notes:

[6] - Non-stratified Log-Rank Test

Secondary: Time to Slow Vital Capacity (SVC) Predicted <70 Percent (%) or Death	
End point title	Time to Slow Vital Capacity (SVC) Predicted <70 Percent (%) or Death

End point description:

SVC was measured using spirometer. Time to SVC predicted <70% or death was reported. Kaplan-Meier estimate was used for analysis. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to SVC predicted <70% or death, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: days				
median (confidence interval 95%)	335 (265 to 441)	358 (283 to 442)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without SVC Predicted <70% or Death

End point title	Percentage of Participants Without SVC Predicted <70% or Death

End point description:

SVC was measured using spirometer. Percentage of Participants Without SVC predicted <70% or death was reported. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to SVC predicted <70% or death, whichever occurred first (up to Month 18)

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: percentage of participants				
number (confidence interval 95%)	28.9 (23 to 35.1)	31.9 (25.6 to 38.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 [7]
Method	Logrank

Notes:

[7] - Stratified Log-Rank test. Stratification criteria: site of onset (bulbar or spinal)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 [8]
Method	Logrank

Notes:

[8] - Non-stratified Log-Rank Test

Secondary: Total ALS FRS-R Global Score

End point title	Total ALS FRS-R Global Score

End point description:

ALS FRS-R scale is a validated rating instrument for monitoring the progression of disability in ALS participants. Participants were asked to rate their functions for the following 12 parameters each on the scale of 0-4 (higher score indicated normal function): speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, respiratory insufficiency. Global score was the sum of individual scores and ranged from 0-48 (higher score indicated normal function). ITT population. 'Number of Subjects Analyzed' = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 9

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	205		
Units: units on a scale				
arithmetic mean (standard deviation)	30.4 (± 8.23)	32.7 (± 7.72)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0184 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	3.49
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[9] - Mixed-effect repeated measures model

Secondary: SVC (in Liters)

End point title	SVC (in Liters)

End point description:

SVC was measured using spirometer. ITT population. 'Number of Subjects Analyzed' = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 9

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	195		
Units: liters				
arithmetic mean (standard deviation)	2.95 (± 1.14)	3.04 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: SVC Percent Predicted

End point title	SVC Percent Predicted

End point description:

SVC was measured using spirometer. Percent predicted SVC was reported. ITT population. 'Number of Subjects Analyzed' = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 9

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	195		
Units: %SVC				
arithmetic mean (standard deviation)	75.5 (± 24.7)	77.9 (± 24.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3838 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	7.24
Variability estimate	Standard error of the mean
Dispersion value	2.55

Notes:

[10] - Mixed-effect repeated measures model

Secondary: McGill Quality of Life (QoL) Scale Score

End point title	McGill Quality of Life (QoL) Scale Score

End point description:

QoL was assessed with the McGill single item questionnaire. The questionnaire required the participant to rate on a visual analog scale of 0 (very bad) to 10 (excellent). ITT population. 'Number of Subjects Analyzed' = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 9

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	202		
Units: units on a scale				
arithmetic mean (standard deviation)	5.25 (± 2)	5.3 (± 2.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9172 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[11] - Mixed-effect repeated measures model

Secondary: Manual Muscle Test (MMT) Global Score

End point title	Manual Muscle Test (MMT) Global Score

End point description:

MMT was performed by trained experienced personnel for 30 items each on a scale of 0-5 (higher score indicated normal function). Global score was the sum of individual scores and ranged from 0-150 (higher score indicated normal function). ITT population. 'Number of Subjects Analyzed' = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 9

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	200		
Units: units on a scale				
arithmetic mean (standard deviation)	109 (± 27.1)	112 (± 27.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TRO19622
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3699 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	8.19
Variability estimate	Standard error of the mean
Dispersion value	2.86

Notes:

[12] - Mixed-effect repeated measures model

Secondary: Percentage of Participants With Non-Invasive Positive Pressure Ventilation (NIPPV)

End point title	Percentage of Participants With Non-Invasive Positive Pressure Ventilation (NIPPV)

End point description:

NIPPV was defined as >23 hours of non-invasive ventilation daily for 14 consecutive days. ITT population. 'n' = participants who were evaluable for this each category for each reporting group respectively.

End point type	Secondary

End point timeframe:

Months 1, 2, 3, 6, 9, 12, 15, 18

End point values	Placebo	TRO19622		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	259		
Units: percentage of participants				
number (not applicable)				
Month 1 (n = 253, 259)	0	0		
Month 2 (n = 248, 248)	0.4	0		
Month 3 (n = 250, 256)	0.4	0		
Month 6 (n = 240, 248)	0	0.8		
Month 9 (n = 222, 227)	0	0		
Month 12 (n = 202, 205)	0.5	0		
Month 15 (n = 177, 181)	1.1	1.7		
Month 18 (n = 152, 164)	0.7	1.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 18 months	
Adverse event reporting additional description:	
Safety population included all participants who had at least one intake of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	V 11.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TRO19622 once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	
Reporting group title	TRO19622
Reporting group description:	
Participants received TRO19622 at a dose of 330 mg once daily orally along with concurrent riluzole at a dose of 50 mg twice daily orally for 18 months.	

Serious adverse events	Placebo	TRO19622	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 253 (25.69%)	68 / 259 (26.25%)	
number of deaths (all causes)	80	79	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine leiomyoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 253 (0.79%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	2 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolism			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mechanical ventilation			
subjects affected / exposed	0 / 253 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Application site inflammation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Application site pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	8 / 253 (3.16%)	14 / 259 (5.41%)	
occurrences causally related to treatment / all	2 / 9	2 / 14	
deaths causally related to treatment / all	0 / 4	1 / 6	
Pulmonary embolism			
subjects affected / exposed	7 / 253 (2.77%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	4 / 7	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 253 (2.37%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	5 / 253 (1.98%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Lung disorder			
subjects affected / exposed	1 / 253 (0.40%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Acute respiratory failure			
subjects affected / exposed	0 / 253 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atelectasis			
subjects affected / exposed	1 / 253 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	1 / 253 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased bronchial secretion			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 253 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchial secretion retention			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocturnal dyspnoea			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract congestion			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 253 (0.00%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep disorder			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			

subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device breakage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint sprain			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning deliberate			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial flutter			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Areflexia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic encephalopathy			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningorrhagia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 253 (0.40%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 253 (0.79%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute abdomen			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Alcoholic liver disease			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 253 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 253 (1.98%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	2 / 253 (0.79%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	3 / 253 (1.19%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	1 / 253 (0.40%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 253 (0.79%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 253 (0.40%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 253 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	TRO19622	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 253 (39.92%)	98 / 259 (37.84%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	19 / 253 (7.51%)	26 / 259 (10.04%)	
occurrences (all)	23	34	

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	13 / 253 (5.14%) 13	7 / 259 (2.70%) 8	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	18 / 253 (7.11%) 20	19 / 259 (7.34%) 23	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	15 / 253 (5.93%) 18 16 / 253 (6.32%) 19	27 / 259 (10.42%) 31 15 / 259 (5.79%) 15	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	15 / 253 (5.93%) 16	7 / 259 (2.70%) 7	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 253 (5.93%) 18 36 / 253 (14.23%) 45	10 / 259 (3.86%) 12 22 / 259 (8.49%) 30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2010	Introduced to implement a validated method of administering study treatments for participants with swallowing difficulties. The method involves administration via the gastrostomy tube to increase participant's comfort and avoid complications associated with swallowing difficulties. The method was verified with treating centers and validated by a steering committee. It was not expected to influence pharmacokinetic parameters.
22 April 2010	Introduced to ensure investigators collected maximum data in the event of premature participant withdrawal for a reason other than death.
06 December 2010	A modification of the text was made to ensure agreement between the specified analysis and the analysis method used to calculate the sample size and power calculation. The term "18 month survival rate" was thus replaced with "overall survival".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported