Clinical trial results:
A Phase 3, Open-Label Extension Study of Tirasemtiv for Patients with Amyotrophic Lateral Sclerosis (ALS) who Completed VITALITY-ALS (CY 4031)

Summary

EudraCT number	2016-002629-13
Trial protocol	IE ES NL BE PT FR GB IT
Global end of trial date	26 October 2018

Results information

Result version number	v1 (current)
This version publication date	05 March 2020
First version publication date	05 March 2020

Trial information

Trial identification

Sponsor protocol code	CY 4033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02936635
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytokinetics, Inc.
Sponsor organisation address	280 East Grand Avenue, South San Francisco, California, United States, 94080
Public contact	Medical Affairs, Cytokinetics, Inc., +1 6506242929, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics, Inc., +1 6506242929, 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	26 October 2018
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	26 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the long-term safety and tolerability of tirasemtiv in patients with ALS.

Protection of trial subjects:

The protocol and consent form were submitted by each investigator to an institutional review board (IRB), an ethics committee (EC), or a research ethics board (REB) for review and approval before study initiation. All amendments to the protocol or revisions to the consent form (if applicable) after initial IRB/EC/REB approval were submitted by the investigator to the IRB/EC/REB for review and approval before implementation. This study was conducted in accordance with the United States Code of Federal Regulations and applicable International Council on Harmonisation guidelines, consistent with Good Clinical Practice (GCP). All patients provided informed written consent before any protocol-specific procedures were performed.

Background therapy:

None

Evidence for comparator:

The CY 4033 trial was an open-label extension study of CY 4031, a randomized, double-blind, controlled study of tirasemtiv versus placebo in patients with ALS. All patients in CY 4033 had completed CY 4031. Following enrollment in CY 4033, patients received tirasemtiv at a dose of 250 mg/day, which was up-titrated to 375 mg/day at Week 4 and then 500 mg/day at Week 6. No comparator arm was used in CY 4033.

Actual start date of recruitment	17 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	United States: 160
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Ireland: 8

Worldwide total number of subjects	280
EEA total number of subjects	68

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)	213
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in patients with amyotrophic lateral sclerosis (ALS) between 17 October 2016 (date first patient enrolled) through 26 October 2018 (date last patient completed) at 69 sites in Belgium, Canada, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, the United Kingdom, and the United States.

Pre-assignment

Screening details:

280 patients who had completed CY 4031 enrolled in CY 4033. Patients were categorized by treatment received in CY 4031. The Delayed Start treatment group (n=115) included patients who received placebo in CY 4031 and tirasemtiv in CY 4033. The Early Start treatment group (n=165) included patients who received tirasemtiv in both CY 4031 and CY 4033.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Delayed Start Treatment

Arm description:

The Delayed Start Treatment group consisted of patients who received placebo in CY 4031 and tirasemtiv in CY 4033.

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:

Tirasemtiv tablets were administered orally, twice daily.

Arm title	Early Start Treatment

Arm description:

The Early Start Treatment group consisted of patients who received tirasemtiv in both CY 4031 and CY 4033.

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:

Tirasemtiv tablets were administered orally, twice daily.

Number of subjects in period 1	Delayed Start Treatment	Early Start Treatment
Started	115	165
Completed	0	0
Not completed	115	165
Adverse event, serious fatal	9	15
Consent withdrawn by subject	8	15
Physician decision	2	9
Adverse event, non-fatal	43	25
Various reasons	31	65
Progressive disease	10	18
Sponsor discretion	10	16
Lost to follow-up	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Delayed Start Treatment
Reporting group description:	
The Delayed Start Treatment group consisted of patients who received placebo in CY 4031 and tirasemtiv in CY 4033.	
Reporting group title	Early Start Treatment
Reporting group description:	
The Early Start Treatment group consisted of patients who received tirasemtiv in both CY 4031 and CY 4033.	

Reporting group values	Delayed Start Treatment	Early Start Treatment	Total
Number of subjects	115	165	280
Age categorical Units: Subjects			
Adults (18-64 years)	89	124	213
From 65-84 years	26	41	67
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	37	46	83
Male	78	119	197

End points

End points reporting groups

Reporting group title	Delayed Start Treatment
Reporting group description:	
The Delayed Start Treatment group consisted of patients who received placebo in CY 4031 and tirasemtiv in CY 4033.	
Reporting group title	Early Start Treatment
Reporting group description:	
The Early Start Treatment group consisted of patients who received tirasemtiv in both CY 4031 and CY 4033.	

Primary: The long-term safety and tolerability of tirasemtiv as measured by the incidence of adverse events

End point title	The long-term safety and tolerability of tirasemtiv as measured by the incidence of adverse events[1]
End point description:	
End point type	Primary
End point timeframe:	
From the first administration of tirasemtiv through 28 days after the patient's last dose	
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: The primary objective of this extension study was to evaluate the long-term safety and tolerability of open-label tirasemtiv in patients who had completed participation in CY 4031. As such, no formal statistical hypothesis testing or sample size calculation was conducted. The primary endpoint of incidence of adverse events was summarized using descriptive statistics.	

End point values	Delayed Start Treatment	Early Start Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	165		
Units: Percent of patients				
number (not applicable)	97.4	95.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from CY 4031 Baseline in Percent Predicted Slow Vital Capacity to Week 24 in CY 4033

End point title	Change from CY 4031 Baseline in Percent Predicted Slow Vital Capacity to Week 24 in CY 4033
End point description:	
Change from baseline in percent predicted slow vital capacity. Relative difference between groups (Early Start versus Delayed Start treatment groups).	
End point type	Secondary

End point timeframe:

Change from baseline in CY 4031 to Week 24 in CY 4033

End point values	Delayed Start Treatment	Early Start Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[2]	94[3]		
Units: Percent predicted slow vital capacity				
least squares mean (standard error)	-28.79 (± 2.845)	-32.69 (± 2.285)		

Notes:

[2] - Patients who received at least 1 dose of tirasemtiv and had a Week 24 slow vital capacity assessment

[3] - Patients who received at least 1 dose of tirasemtiv and had a Week 24 slow vital capacity assessment

Statistical analyses

Statistical analysis title	Comparison of changes from baseline
Statistical analysis description:	
Difference of LS means (Early Start minus Delayed Start)	
Comparison groups	Delayed Start Treatment v Early Start Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2821
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.035
upper limit	3.23
Variability estimate	Standard error of the mean
Dispersion value	3.619

Secondary: Change from CY 4031 Baseline in Percent Predicted Slow Vital Capacity to Week 48 in CY 4033

End point title	Change from CY 4031 Baseline in Percent Predicted Slow Vital Capacity to Week 48 in CY 4033

End point description:

Change from baseline in percent predicted slow vital capacity. Relative difference between groups (Early Start versus Delayed Start treatment groups).

End point type	Secondary

End point timeframe:

Change from baseline in CY 4031 to Week 48 in CY 4033

End point values	Delayed Start Treatment	Early Start Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[4]	45[5]		
Units: Percent predicted slow vital capacity				
least squares mean (standard error)	-35.55 (± 3.332)	-40.87 (± 2.667)		

Notes:

[4] - Patients who received at least 1 dose of tirasemtiv and had a Week 48 slow vital capacity assessment

[5] - Patients who received at least 1 dose of tirasemtiv and had a Week 48 slow vital capacity assessment

Statistical analyses

Statistical analysis title	Comparison of changes from baseline
Statistical analysis description:	
Difference of LS means (Early Start minus Delayed Start)	
Comparison groups	Delayed Start Treatment v Early Start Treatment
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2118
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.711
upper limit	3.067
Variability estimate	Standard error of the mean
Dispersion value	4.242

Secondary: Change from CY 4031 Baseline in ALS Functional Rating Scale – Revised (ALSFRS-R) Total Score at Week 24

End point title	Change from CY 4031 Baseline in ALS Functional Rating Scale – Revised (ALSFRS-R) Total Score at Week 24
End point description:	
Change from baseline in ALSFRS-R total score. Relative difference between groups (Early Start versus Delayed Start treatment groups).	
End point type	Secondary
End point timeframe:	
Change from baseline in CY 4031 to Week 24 in CY 4033	

End point values	Delayed Start Treatment	Early Start Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75[6]	120[7]		
Units: ALSFRS-R Total Score				
least squares mean (standard error)	-13.78 (± 0.934)	-14.35 (± 0.767)		

Notes:

[6] - Patients who received at least 1 dose of tirasemtiv and had a Week 24 slow vital capacity assessment

[7] - Patients who received at least 1 dose of tirasemtiv and had a Week 24 slow vital capacity assessment

Statistical analyses

Statistical analysis title	Comparison of changes from baseline
Statistical analysis description:	
Difference of LS means (Early Start minus Delayed Start)	
Comparison groups	Delayed Start Treatment v Early Start Treatment
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6354
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.946
upper limit	1.801
Variability estimate	Standard error of the mean
Dispersion value	1.205

Secondary: Change from CY 4031 Baseline in ALSFRS-R Total Score at Week 48

End point title	Change from CY 4031 Baseline in ALSFRS-R Total Score at Week 48
End point description:	
Change from baseline in ALSFRS-R total score. Relative difference between groups (Early Start versus Delayed Start treatment groups).	
End point type	Secondary
End point timeframe:	
Change from baseline in CY 4031 to Week 48 in CY 4033	

End point values	Delayed Start Treatment	Early Start Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[8]	62[9]		
Units: ALSFRS-R Total Score				
least squares mean (standard error)	-17.61 (± 1.171)	-17.82 (± 0.956)		

Notes:

[8] - Patients who received at least 1 dose of tirasemtiv and had a Week 48 slow vital capacity assessment

[9] - Patients who received at least 1 dose of tirasemtiv and had a Week 48 slow vital capacity assessment

Statistical analyses

Statistical analysis title	Comparison of changes from baseline
Statistical analysis description:	
Difference of LS means (Early Start minus Delayed Start)	
Comparison groups	Early Start Treatment v Delayed Start Treatment
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8887
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.186
upper limit	2.763
Variability estimate	Standard error of the mean
Dispersion value	1.509

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each patient, adverse events were collected from the first administration of tirasemtiv through 28 days after the last dose of tirasemtiv.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Delayed Start Treatment

Reporting group description:

The Delayed Start Treatment group consisted of patients who received placebo in CY 4031 and tirasemtiv in CY 4033.

Reporting group title	Early Start Treatment

Reporting group description:

The Early Start Treatment group consisted of patients who received tirasemtiv in both CY 4031 and CY 4033.

Reporting group title	Total

Reporting group description:

All enrolled patients (those in the Delayed Start Treatment group + those in the Early Start Treatment group)

Serious adverse events	Delayed Start Treatment	Early Start Treatment	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 115 (27.83%)	53 / 165 (32.12%)	85 / 280 (30.36%)
number of deaths (all causes)	16	27	43
number of deaths resulting from adverse events	16	27	43
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 115 (0.87%)	2 / 165 (1.21%)	3 / 280 (1.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Euthanasia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Asthenia			

subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeling abnormal			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	6 / 115 (5.22%)	8 / 165 (4.85%)	14 / 280 (5.00%)
occurrences causally related to treatment / all	0 / 6	0 / 8	0 / 14
deaths causally related to treatment / all	0 / 6	0 / 6	0 / 12
Pneumonia aspiration			
subjects affected / exposed	2 / 115 (1.74%)	7 / 165 (4.24%)	9 / 280 (3.21%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Pulmonary embolism			
subjects affected / exposed	2 / 115 (1.74%)	4 / 165 (2.42%)	6 / 280 (2.14%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	2 / 115 (1.74%)	1 / 165 (0.61%)	3 / 280 (1.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Obstructive airways disorder			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bronchial secretion retention			
subjects affected / exposed	0 / 115 (0.00%)	3 / 165 (1.82%)	3 / 280 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 115 (2.61%)	1 / 165 (0.61%)	4 / 280 (1.43%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	2 / 115 (1.74%)	0 / 165 (0.00%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			

subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased bronchial secretion			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract congestion			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	2 / 115 (1.74%)	0 / 165 (0.00%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Traumatic fracture			
subjects affected / exposed	1 / 115 (0.87%)	3 / 165 (1.82%)	4 / 280 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subdural haematoma			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 115 (0.87%)	2 / 165 (1.21%)	3 / 280 (1.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 3
Cardio-respiratory arrest			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Acute myocardial infarction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	4 / 115 (3.48%)	13 / 165 (7.88%)	17 / 280 (6.07%)
occurrences causally related to treatment / all	0 / 4	0 / 14	0 / 18
deaths causally related to treatment / all	0 / 4	0 / 11	0 / 15
Dizziness			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoaesthesia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 115 (0.00%)	2 / 165 (1.21%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 115 (1.74%)	3 / 165 (1.82%)	5 / 280 (1.79%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cholelithiasis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 115 (0.00%)	9 / 165 (5.45%)	9 / 280 (3.21%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Lobar pneumonia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung infection			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bronchitis			
subjects affected / exposed	0 / 115 (0.00%)	2 / 165 (1.21%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 115 (0.87%)	1 / 165 (0.61%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper respiratory tract infection			
subjects affected / exposed	2 / 115 (1.74%)	0 / 165 (0.00%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 165 (0.00%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 165 (0.61%)	1 / 280 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 115 (0.00%)	2 / 165 (1.21%)	2 / 280 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Delayed Start Treatment	Early Start Treatment	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 115 (96.52%)	155 / 165 (93.94%)	266 / 280 (95.00%)
Investigations			
Weight decreased			
subjects affected / exposed	13 / 115 (11.30%)	9 / 165 (5.45%)	22 / 280 (7.86%)
occurrences (all)	15	9	24
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	22 / 115 (19.13%)	23 / 165 (13.94%)	45 / 280 (16.07%)
occurrences (all)	44	45	89
Contusion			
subjects affected / exposed	11 / 115 (9.57%)	13 / 165 (7.88%)	24 / 280 (8.57%)
occurrences (all)	17	20	37
Skin abrasion			
subjects affected / exposed	9 / 115 (7.83%)	4 / 165 (2.42%)	13 / 280 (4.64%)
occurrences (all)	11	9	20
Post-traumatic pain			
subjects affected / exposed	6 / 115 (5.22%)	4 / 165 (2.42%)	10 / 280 (3.57%)
occurrences (all)	9	4	13
Nervous system disorders			
Dizziness			
subjects affected / exposed	49 / 115 (42.61%)	44 / 165 (26.67%)	93 / 280 (33.21%)
occurrences (all)	73	63	136
Somnolence			
subjects affected / exposed	28 / 115 (24.35%)	27 / 165 (16.36%)	55 / 280 (19.64%)
occurrences (all)	33	35	68
Headache			
subjects affected / exposed	8 / 115 (6.96%)	14 / 165 (8.48%)	22 / 280 (7.86%)
occurrences (all)	8	17	25
Dysarthria			
subjects affected / exposed	7 / 115 (6.09%)	6 / 165 (3.64%)	13 / 280 (4.64%)
occurrences (all)	9	7	16
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	42 / 115 (36.52%)	51 / 165 (30.91%)	93 / 280 (33.21%)
occurrences (all)	58	65	123
Asthenia			
subjects affected / exposed	14 / 115 (12.17%)	8 / 165 (4.85%)	22 / 280 (7.86%)
occurrences (all)	17	11	28
Oedema peripheral			
subjects affected / exposed	6 / 115 (5.22%)	6 / 165 (3.64%)	12 / 280 (4.29%)
occurrences (all)	8	6	14
Feeling abnormal			
subjects affected / exposed	6 / 115 (5.22%)	4 / 165 (2.42%)	10 / 280 (3.57%)
occurrences (all)	7	6	13
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	20 / 115 (17.39%)	33 / 165 (20.00%)	53 / 280 (18.93%)
occurrences (all)	26	38	64
Nausea			
subjects affected / exposed	19 / 115 (16.52%)	22 / 165 (13.33%)	41 / 280 (14.64%)
occurrences (all)	21	28	49
Dysphagia			
subjects affected / exposed	12 / 115 (10.43%)	9 / 165 (5.45%)	21 / 280 (7.50%)
occurrences (all)	13	9	22
Salivary hypersecretion			
subjects affected / exposed	8 / 115 (6.96%)	10 / 165 (6.06%)	18 / 280 (6.43%)
occurrences (all)	9	12	21
Diarrhoea			
subjects affected / exposed	3 / 115 (2.61%)	12 / 165 (7.27%)	15 / 280 (5.36%)
occurrences (all)	3	14	17
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 115 (5.22%)	4 / 165 (2.42%)	10 / 280 (3.57%)
occurrences (all)	6	4	10
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	16 / 115 (13.91%)	16 / 165 (9.70%)	32 / 280 (11.43%)
occurrences (all)	17	20	37

Cough			
subjects affected / exposed	7 / 115 (6.09%)	7 / 165 (4.24%)	14 / 280 (5.00%)
occurrences (all)	9	9	18
Choking			
subjects affected / exposed	7 / 115 (6.09%)	4 / 165 (2.42%)	11 / 280 (3.93%)
occurrences (all)	8	5	13
Increased upper airway secretion			
subjects affected / exposed	6 / 115 (5.22%)	5 / 165 (3.03%)	11 / 280 (3.93%)
occurrences (all)	6	5	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 115 (13.91%)	14 / 165 (8.48%)	30 / 280 (10.71%)
occurrences (all)	16	16	32
Anxiety			
subjects affected / exposed	16 / 115 (13.91%)	12 / 165 (7.27%)	28 / 280 (10.00%)
occurrences (all)	19	13	32
Depression			
subjects affected / exposed	16 / 115 (13.91%)	10 / 165 (6.06%)	26 / 280 (9.29%)
occurrences (all)	19	11	30
Confusional state			
subjects affected / exposed	8 / 115 (6.96%)	8 / 165 (4.85%)	16 / 280 (5.71%)
occurrences (all)	10	8	18
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	16 / 115 (13.91%)	33 / 165 (20.00%)	49 / 280 (17.50%)
occurrences (all)	25	45	70
Muscle spasms			
subjects affected / exposed	18 / 115 (15.65%)	10 / 165 (6.06%)	28 / 280 (10.00%)
occurrences (all)	20	12	32
Back pain			
subjects affected / exposed	9 / 115 (7.83%)	7 / 165 (4.24%)	16 / 280 (5.71%)
occurrences (all)	9	7	16
Pain in extremity			
subjects affected / exposed	4 / 115 (3.48%)	9 / 165 (5.45%)	13 / 280 (4.64%)
occurrences (all)	6	12	18
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	8 / 115 (6.96%)	18 / 165 (10.91%)	26 / 280 (9.29%)
occurrences (all)	10	22	32
Urinary tract infection			
subjects affected / exposed	5 / 115 (4.35%)	10 / 165 (6.06%)	15 / 280 (5.36%)
occurrences (all)	6	10	16
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 115 (13.91%)	13 / 165 (7.88%)	29 / 280 (10.36%)
occurrences (all)	19	15	34

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported