Clinical trial results:
A Phase IIb, multi-national, double-blind, randomised, placebo-controlled study to evaluate the safety, tolerability and efficacy of CK-2017357 in patients with amyotrophic lateral sclerosis (ALS)

Summary

EudraCT number	2012-004987-23
Trial protocol	IE GB DE NL ES
Global end of trial date	21 March 2014

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020

Trial information

Trial identification

Sponsor protocol code	CY 4026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709149
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., 001 6506242929, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics, Inc., 001 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	21 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of CK-2017357 (hereafter referred to as tirasemtiv) versus placebo on the ALS Functional Rating Scale-Revised (ALSFRS-R) total score when administered twice daily at each patient's maximum tolerated dose, up to a maximum of 500 mg daily.

Protection of trial subjects:

The study was conducted in accordance with the Code of Federal Regulations (CFR) governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Applications (21 CFR 312), and Applications for Food and Drug Administration Approval to Market a New Drug (21 CFR 314), as appropriate. These sections of United States Title 21 CFR, along with the applicable International Conference on Harmonization (ICH) Guidelines, are commonly known as Good Clinical Practices (GCP), which are consistent with the Declaration of Helsinki, 1996.

Background therapy:

During the open-label portion of the study, patients taking riluzole prior to study entry continued riluzole from their personal supply at a dose of 50 mg once daily (in the morning). Patients not taking riluzole prior to the study did not receive riluzole during the study.

During the double-blind portion of the study, patients taking riluzole prior to study entry continued riluzole treatment during the 12-week double-blind portion of the study as follows: patients randomized to placebo took riluzole 50 mg from their personal supply once daily (in the morning) and over-encapsulated riluzole 50 mg, supplied by the sponsor, once daily (in the evening); patients randomized to tirasemtiv took riluzole 50 mg from their personal supply once daily (in the morning) and placebo to match over-encapsulated riluzole, supplied by the sponsor, once daily (in the evening). Patients not taking riluzole prior to the study did not receive riluzole during the study.

Evidence for comparator: -

Actual start date of recruitment	23 October 2012
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: 409
Country: Number of subjects enrolled	Canada: 104
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Ireland: 13

Worldwide total number of subjects	711
EEA total number of subjects	198

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)	511
From 65 to 84 years	197
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients with familial or sporadic ALS were enrolled at 73 sites in Canada, France, Germany, Ireland, Netherlands, Spain, the United Kingdom, and the United States. The first patient was screened on 23 October 2012 and the last subject completed on 21 March 2014.

Pre-assignment

Screening details:

A total of 711 patients were enrolled in the study and began treatment with open-label tirasemtiv during the 7-day lead-in phase of the study. Patients who completed this phase were randomized (1:1) to receive either placebo (N=295) or tirasemtiv (N=301) in the double-blind treatment period.

Period 1

Period 1 title	Open-label Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label lead-in treatment: Tirasemtiv

Arm description:

During the open-label phase, all 711 enrolled patients initiated treatment with tirasemtiv immediate release 125 mg tablets, administered orally twice daily (for a total daily dose of 250 mg) for 7 days.

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	CK-2017357
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tirasemtiv immediate release 125 mg tablets were administered orally twice daily (for a total daily dose of 250 mg) for 7 days.

Number of subjects in period 1	Open-label lead-in treatment: Tirasemtiv
Started	711
Completed	596
Not completed	115
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Adverse event, non-fatal	109
Protocol deviation	3

Period 2

Period 2 title	Double-blind 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	Double-blind treatment: Tirasemtiv

Arm description:

Patients started at a dose of 125 mg twice daily, then up-titrated, over 3 to 4 weeks, to a dose of 250 mg twice daily (for a total daily dose of 500 mg), depending on tolerability. Patients remained at their last tolerated dose for the remainder of the study.

Arm type	Experimental
Investigational medicinal product name	Tirasemtiv
Investigational medicinal product code	CK-2017357
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated for a total of 12 weeks with a dose-titration phase lasting approximately 3 to 4 weeks, followed by a maximum tolerated dose phase lasting for the remainder of the study. During the first week of the dose-titration phase, patients took 1 tirasemtiv tablet (125 mg) twice daily (for a total daily dose of 250 mg) for 7 days depending on tolerability. During the second week of dose-titration, the tirasemtiv dose was increased to 1 tablet (125 mg) in the morning and 2 tablets (250 mg) in the evening (for a total daily dose of 375 mg) for 7 days depending on tolerability. During the third week of dose-titration, the dose was increased to 2 tablets (250 mg) twice daily (for a total daily dose of 500 mg) for 7 days depending on tolerability. The start of the fourth week represented the end of the dose-titration phase and the start of the maximum tolerated dose phase. Patients remained on their maximum tolerated dose for the remainder of the study.

Arm title	Double-blind treatment: Placebo

Arm description:

Patients started taking 1 placebo table twice daily, then up-titrated, over 3 to 4 weeks, to 2 placebo tablets twice daily. Patients remained at their last tolerated dose for the remainder of the study.

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

Dosage and administration details:

Patients were treated for a total of 12 weeks with a dose-titration phase lasting approximately 3 to 4 weeks, followed by a maximum tolerated dose phase lasting for the remainder of the study. During the first week of the dose-titration phase, patients took 1 placebo tablet twice daily for 7 days. During the second week of dose-titration, patients took 1 placebo tablet in the morning and 2 placebo tablets in the evening for 7 days. During the third week of dose-titration, patients took 2 placebo tablets twice daily for 7 days. The start of the fourth week represented the end of the dose-titration phase and the start of the maximum tolerated dose phase. Patients remained on their maximum tolerated dose for the remainder of the study.

Number of subjects in period 2	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo
Started	301	295
Completed	204	269
Not completed	97	26
Adverse event, serious fatal	-	2
Consent withdrawn by subject	12	7
Adverse event, non-fatal	78	12
Investigator Judgment	5	2
Unspecified	2	1
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Open-label Phase
Reporting group description:	
All 711 enrolled patients started in the open-label phase and initiated open-label tirasemtiv treatment.	

Reporting group values	Open-label Phase	Total	
Number of subjects	711	711	
Age categorical Units: Subjects			
Adults (18-64 years)	511	511	
From 65-84 years	197	197	
85 years and over	3	3	
Age continuous Units: years			
arithmetic mean	57.5		
standard deviation	± 10.98	-	
Gender categorical Units: Subjects			
Female	226	226	
Male	485	485	

End points

End points reporting groups

Reporting group title	Open-label lead-in treatment: Tirasemtiv
Reporting group description:	
During the open-label phase, all 711 enrolled patients initiated treatment with tirasemtiv immediate release 125 mg tablets, administered orally twice daily (for a total daily dose of 250 mg) for 7 days.	
Reporting group title	Double-blind treatment: Tirasemtiv
Reporting group description:	
Patients started at a dose of 125 mg twice daily, then up-titrated, over 3 to 4 weeks, to a dose of 250 mg twice daily (for a total daily dose of 500 mg), depending on tolerability. Patients remained at their last tolerated dose for the remainder of the study.	
Reporting group title	Double-blind treatment: Placebo
Reporting group description:	
Patients started taking 1 placebo table twice daily, then up-titrated, over 3 to 4 weeks, to 2 placebo tablets twice daily. Patients remained at their last tolerated dose for the remainder of the study.	

Primary: Change from Baseline in ALSFRS-R Total Score to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in ALSFRS-R Total Score to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment
End point description:	
The ALSFRS-R is used to measure the progression and severity of disease; it 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 is score from 0 (indicating incapable or dependent) to 4 (normal). The total score ranged from 0 to 48, with higher scores reflecting more normal function and lower scores reflecting more impaired function. For analysis of the primary endpoint, changes from baseline in ALSFRS-R total score at Visits 6 (Week 8) and 7 (Week 12) were averaged.	
End point type	Primary
End point timeframe:	
End of Weeks 8 and 12	

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: score on a scale				
least squares mean (standard error)	-2.98 (± 0.277)	-2.4 (± 0.246)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in ALSFRS-R Score
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment:

	Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.114
Method	Repeated-measures mixed model
Parameter estimate	LS Mean difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.366

Notes:

[1] - The analysis was performed using a repeated-measures mixed model which included terms of treatment, baseline, pooled site, visit, and riluzole use/non-use, as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix.

Secondary: Change from Baseline in the Maximum Voluntary Ventilation (MVV) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in the Maximum Voluntary Ventilation (MVV) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point description:

MVV was measured as the volume of air (in liters) that could be exhaled during 12 seconds of rapid deep breathing. For analysis purposes, the measured volume was extrapolated to 1 minute (to give units of L/min).

End point type	Secondary

End point timeframe:

End of Weeks 8 and 12

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: Litres per (/) minute				
least squares mean (standard error)	-3.79 (± 1.497)	-4.27 (± 1.332)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in MVV
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo

Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8083
Method	Repeated measures model

Secondary: Change from Baseline in Sniff Nasal Inspiratory Pressure (SNIP) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in Sniff Nasal Inspiratory Pressure (SNIP) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point description:

SNIP was measured at functional residual capacity (the bottom of the tidal breathing cycle) through one plugged nostril while the other remained open. A forceful, maximal inspiratory sniff was performed and a peak pressure value reported. The best result (ie, the highest number) from 5 tests was recorded as the SNIP.

End point type	Secondary

End point timeframe:

End of Weeks 8 and 12

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: centimetres H2O				
least squares mean (standard error)	-4.29 (± 1.243)	-0.89 (± 1.103)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in SNIP
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0372
Method	Repeated measures model

Secondary: Change from Baseline in Percent Predicted Slow Vital Capacity (SVC) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in Percent Predicted Slow Vital Capacity (SVC) to the Average of Values Obtained at the End of Weeks 8

	and 12 of Double-blind Treatment

End point description:

SVC was measured using a spirometer (in units of liters). Following 3 to 5 breaths at rest, patients were instructed to take as deep an inspiration as possible followed by a maximum exhalation (blowing out all the air in their lungs). Values obtained were converted to percent predicted values (ie, the test result as a percent of predicted values for the patients of similar demographic and baseline characteristics [eg, height, age, sex]).

End point type	Secondary

End point timeframe:

End of Weeks 8 and 12

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: percent				
least squares mean (standard error)	-2.98 (± 0.78)	-7.24 (± 0.691)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in SVC
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Repeated measures model

Secondary: Change from Baseline in Maximum Handgrip Strength in the Weaker Hand to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in Maximum Handgrip Strength in the Weaker Hand to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point description:

Maximum handgrip strength was measured using an electronic hand dynamometer. Patients were asked to squeeze the device with the maximum possible force. Maximum handgrip strength was recorded for both the right and left hand: the greater of two attempts for each hand was used. Data presented are for the qualifying weaker hand.

End point type	Secondary

End point timeframe:

End of Weeks 8 and 12

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: pound				
least squares mean (standard error)	-2.78 (± 0.714)	-3.54 (± 0.64)		

Statistical analyses

Statistical analysis title	Analysis of Change in Maximum Handgrip Strength
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4328
Method	Repeated measures model

Secondary: Change from Baseline in Muscle Strength Mega-Score to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in Muscle Strength Mega-Score to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point description:

A hand held dynamometer (HHD) was used to measure muscle strength. The following muscle groups were assessed: elbow flexion (bilateral), wrist extension (bilateral), knee extension (bilateral), and ankle dorsiflexion (bilateral). A muscle strength mega-score was calculated as the average of responses to all tested muscles as well as handgrip strength.

End point type	Secondary

End point timeframe:

End of Weeks 8 and 12

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: percent				
least squares mean (standard error)	-9.1 (± 2.425)	-10.71 (± 2.108)		

Statistical analyses

Statistical analysis title	Analysis of Muscle Strength Mega-Score
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6166
Method	Repeated measures model

Secondary: Change from Baseline in Handgrip Fatigability (at 60% of Target in Weaker Hand) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment

End point title	Change from Baseline in Handgrip Fatigability (at 60% of Target in Weaker Hand) to the Average of Values Obtained at the End of Weeks 8 and 12 of Double-blind Treatment
End point description:	
End point type	Secondary
End point timeframe: End of Weeks 8 and 12	

End point values	Double-blind treatment: Tirasemtiv	Double-blind treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	210		
Units: seconds				
least squares mean (standard error)	2.01 (± 3.331)	1.76 (± 2.863)		

Statistical analyses

Statistical analysis title	Analysis of Handgrip Fatigability
Comparison groups	Double-blind treatment: Tirasemtiv v Double-blind treatment: Placebo

Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9546
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	8.9
Variability estimate	Standard error of the mean
Dispersion value	4.399

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from the first dose of open-label study drug through 30 days after the last dose of study
drug or Week 16, whichever was earlier.

Adverse event reporting additional description:

An AE was treatment-emergent if it started or worsened in severity after the first dose of study drug (during either open-label or double-blind treatment). If an AE started in the open-label phase and continued into the double-blind phase for more than 96 hours, it was assigned an onset of 96 hours after the first dose of double-blind study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Open-label lead-in treatment: Tirasemtiv

Reporting group description:

Tirasemtiv immediate release 125 mg tablets administered orally twice daily (for a total daily dose of 250 mg) for 7 days.

Reporting group title	Double-blind treatment: Placebo

Reporting group description:

Patients started taking 1 placebo tablet twice daily, then up-titrated, over 3 to 4 weeks, to 2 placebo tablets twice daily. Patients remained at their last tolerated dose for the remainder of the study.

Reporting group title	Double-blind treatment: Tirasemtiv

Reporting group description:

Patients started at a dose of 125 mg twice daily, then up-titrated, over 3 to 4 weeks, to a dose of 250 mg twice daily (for a total daily dose of 500 mg), depending on tolerability. Patients remained at their last tolerated dose for the remainder of the study.

Serious adverse events	Open-label lead-in treatment: Tirasemtiv	Double-blind treatment: Placebo	Double-blind treatment: Tirasemtiv
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 711 (1.83%)	16 / 295 (5.42%)	27 / 301 (8.97%)
number of deaths (all causes)	2	3	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 711 (0.14%)	0 / 295 (0.00%)	0 / 301 (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
Prostate cancer			

subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 711 (0.14%)	0 / 295 (0.00%)	0 / 301 (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
Joint dislocation			
subjects affected / exposed	1 / 711 (0.14%)	0 / 295 (0.00%)	0 / 301 (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
Face injury			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia paroxysmal			
subjects affected / exposed	1 / 711 (0.14%)	0 / 295 (0.00%)	0 / 301 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	1 / 301 (0.33%)
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	0 / 711 (0.00%)	1 / 295 (0.34%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 711 (0.14%)	0 / 295 (0.00%)	0 / 301 (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 accident			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paresis			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal haematoma			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			

subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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
Dysphagia			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	1 / 711 (0.14%)	1 / 295 (0.34%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 711 (0.14%)	1 / 295 (0.34%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 711 (0.28%)	1 / 295 (0.34%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 711 (0.00%)	3 / 295 (1.02%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 711 (0.28%)	0 / 295 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 711 (0.28%)	0 / 295 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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

Musculoskeletal and connective tissue disorders			
Spinal column stenosis			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 711 (0.14%)	1 / 295 (0.34%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Kidney infection			
subjects affected / exposed	0 / 711 (0.00%)	0 / 295 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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
Post procedural infection			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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
Respiratory tract infection			
subjects affected / exposed	0 / 711 (0.00%)	1 / 295 (0.34%)	0 / 301 (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

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

Non-serious adverse events	Open-label lead-in treatment: Tirasemtiv	Double-blind treatment: Placebo	Double-blind treatment: Tirasemtiv
Total subjects affected by non-serious adverse events			
subjects affected / exposed	523 / 711 (73.56%)	257 / 295 (87.12%)	290 / 301 (96.35%)
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	6 / 711 (0.84%)	25 / 295 (8.47%)	22 / 301 (7.31%)
occurrences (all)	6	45	32
Excoriation			
subjects affected / exposed	2 / 711 (0.28%)	15 / 295 (5.08%)	17 / 301 (5.65%)
occurrences (all)	2	21	21
Laceration			
subjects affected / exposed	6 / 711 (0.84%)	11 / 295 (3.73%)	18 / 301 (5.98%)
occurrences (all)	6	12	20
Nervous system disorders			
Dizziness			
subjects affected / exposed	291 / 711 (40.93%)	58 / 295 (19.66%)	153 / 301 (50.83%)
occurrences (all)	337	65	266
Headache			
subjects affected / exposed	30 / 711 (4.22%)	33 / 295 (11.19%)	54 / 301 (17.94%)
occurrences (all)	30	47	68
Dysarthria			
subjects affected / exposed	13 / 711 (1.83%)	7 / 295 (2.37%)	23 / 301 (7.64%)
occurrences (all)	13	7	30
Muscle contractions involuntary			
subjects affected / exposed	15 / 711 (2.11%)	8 / 295 (2.71%)	16 / 301 (5.32%)
occurrences (all)	17	8	17
Somnolence			
subjects affected / exposed	50 / 711 (7.03%)	11 / 295 (3.73%)	39 / 301 (12.96%)
occurrences (all)	54	12	46
Tremor			
subjects affected / exposed	8 / 711 (1.13%)	7 / 295 (2.37%)	16 / 301 (5.32%)
occurrences (all)	8	10	21
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 711 (5.63%)	37 / 295 (12.54%)	48 / 301 (15.95%)
occurrences (all)	41	39	60
Fatigue			
subjects affected / exposed	111 / 711 (15.61%)	42 / 295 (14.24%)	100 / 301 (33.22%)
occurrences (all)	116	44	126
Oedema peripheral			

subjects affected / exposed	5 / 711 (0.70%)	17 / 295 (5.76%)	18 / 301 (5.98%)
occurrences (all)	5	19	20
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 711 (1.55%)	17 / 295 (5.76%)	19 / 301 (6.31%)
occurrences (all)	11	19	21
Diarrhoea			
subjects affected / exposed	10 / 711 (1.41%)	17 / 295 (5.76%)	22 / 301 (7.31%)
occurrences (all)	10	18	26
Nausea			
subjects affected / exposed	77 / 711 (10.83%)	23 / 295 (7.80%)	66 / 301 (21.93%)
occurrences (all)	86	28	91
Dysphagia			
subjects affected / exposed	6 / 711 (0.84%)	10 / 295 (3.39%)	15 / 301 (4.98%)
occurrences (all)	6	11	15
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 711 (0.14%)	14 / 295 (4.75%)	18 / 301 (5.98%)
occurrences (all)	1	14	18
Dyspnoea			
subjects affected / exposed	11 / 711 (1.55%)	8 / 295 (2.71%)	25 / 301 (8.31%)
occurrences (all)	15	8	32
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 711 (0.42%)	3 / 295 (1.02%)	17 / 301 (5.65%)
occurrences (all)	3	3	21
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 711 (2.11%)	13 / 295 (4.41%)	20 / 301 (6.64%)
occurrences (all)	16	13	22
Confusional state			
subjects affected / exposed	17 / 711 (2.39%)	3 / 295 (1.02%)	32 / 301 (10.63%)
occurrences (all)	20	4	36
Depression			
subjects affected / exposed	8 / 711 (1.13%)	10 / 295 (3.39%)	16 / 301 (5.32%)
occurrences (all)	8	10	18

Insomnia			
subjects affected / exposed	16 / 711 (2.25%)	12 / 295 (4.07%)	31 / 301 (10.30%)
occurrences (all)	18	12	32
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 711 (1.27%)	20 / 295 (6.78%)	15 / 301 (4.98%)
occurrences (all)	9	20	17
Muscle spasms			
subjects affected / exposed	30 / 711 (4.22%)	16 / 295 (5.42%)	45 / 301 (14.95%)
occurrences (all)	33	23	57
Muscular weakness			
subjects affected / exposed	21 / 711 (2.95%)	20 / 295 (6.78%)	34 / 301 (11.30%)
occurrences (all)	22	23	43
Musculoskeletal pain			
subjects affected / exposed	6 / 711 (0.84%)	17 / 295 (5.76%)	9 / 301 (2.99%)
occurrences (all)	7	19	12
Pain in extremity			
subjects affected / exposed	8 / 711 (1.13%)	17 / 295 (5.76%)	14 / 301 (4.65%)
occurrences (all)	8	21	16
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 711 (0.98%)	19 / 295 (6.44%)	19 / 301 (6.31%)
occurrences (all)	7	22	20
Upper respiratory tract infection			
subjects affected / exposed	3 / 711 (0.42%)	15 / 295 (5.08%)	9 / 301 (2.99%)
occurrences (all)	3	16	11
Urinary tract infection			
subjects affected / exposed	5 / 711 (0.70%)	14 / 295 (4.75%)	17 / 301 (5.65%)
occurrences (all)	5	17	18
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 711 (3.23%)	9 / 295 (3.05%)	30 / 301 (9.97%)
occurrences (all)	25	10	34

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2013	The major protocol changes were as follows: to increase enrollment up to 500 patients; to amend the inclusion criterion regarding SVC to >50% of predicted for age, height, and sex; to amend the inclusion criterion regarding maximum grip strength to allow up to 50 pounds for females and up to 70 pounds for males; to amend the exclusion criterion to add tizanidine as an exclusionary medication; to amend the exclusion criterion regarding bronchodilator medications to exclude patients requiring frequent use; to add an appendix listing the substrates, inhibitors, and inducers of CYP1A2 and the rationale for including them.
19 July 2013	The major protocol changes were as follows: to increase enrollment to approximately 680 patients (the increased enrollment was intended to reduce the impact of an error in study drug assignment that affected 58 patients initially randomized to and treated with tirasemtiv who were erroneously switched to placebo at Visits 5 and 6); to add an exclusion criterion for patients judged by the Investigator as actively suicidal and a suicide risk; to add a suicidality assessment at each study visit; to update the Statistical Methods section to describe the handling of the 58 affected patients in the statistical analyses and to add the suicidality assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported