Clinical trial results:
Effects of ODM-109 on respiratory function in patients with ALS. A randomised, double blind, placebo-controlled, cross-over, 3-period, multicentre study with open-label follow-up extension

Summary

EudraCT number	2014-004567-21
Trial protocol	IE DE GB NL
Global end of trial date	11 May 2017

Results information

Result version number	v1 (current)
This version publication date	25 May 2018
First version publication date	25 May 2018

Trial information

Trial identification

Sponsor protocol code	3119001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02487407
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orion Pharma
Sponsor organisation address	Orionintie 1, Espoo, Finland, 02200
Public contact	Clinical Trials Information, Orion Corporation Orion Pharma, 358 0104261, clinicaltrials@orionpharma.com
Scientific contact	Clinical Trials Information, Orion Corporation Orion Pharma, 358 0104261, clinicaltrials@orionpharma.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	11 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2017
Global end of trial reached?	Yes
Global end of trial date	11 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate the efficacy of oral levosimendan on respiratory function in patients with Amyotrophic Lateral Sclerosis.

Protection of trial subjects:

The study data was monitored regularly by the Sponsor, and accumulating data were reviewed periodically by an independent Data and Safety Monitoring Board (DSMB). The DSMB were able to amend the study protocol for safety reasons, stop the study or withdraw individual patients from treatment if deemed necessary.
The study included frequent assessment of safety measurements typical of clinical trials, including blood pressure, heart rate 12-lead ECG, 24 hour Holter (ECG) recording, safety laboratory tests and adverse events. These were performed before, during and after study drug treatment
Specific criteria were in place for the withdrawal of patients from study treatment, including increased heart rate (increased >15 bpm from baseline), ventricular tachycardia, atrial fibrillation/flutter, pregnancy and need for invasive ventilator support. The investigator could also withdraw the treatment if considered to be in the best interests of the subject. Patients were free to leave the study at any time but were also withdrawn in the event of a safety finding of clinical concern.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Ireland: 3
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	50
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with amyotrophic lateral sclerosis (ALS) were recruited.

Pre-assignment

Screening details:

Male or female subjects, disease duration from symptom onset 12-48 months before the baseline, written informed consent (IC) obtained. Age at least 18 years, upright slow vital capacity (SVC) between 60-90% of the predicted value for age, height and sex at screening visit, mormal oxygen saturation during daytime, using riluzole.

Period 1

Period 1 title	Cross-over part
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Exactly similar placebo capsules were used, and 1 placebo capsule was given in the evening for the 1 mg treatment group.

Arms

Are arms mutually exclusive?	No
Arm title	Levosimendan 1 mg

Arm description:

1 levosimendan 1 mg capsule in the morning and 1 placebo capsule 12 hours later for 14 days.

Arm type	Experimental
Investigational medicinal product name	Levosimendan 1 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 levosimendan 1 mg capsule in the morning for 14 days.

Arm title	Levosimendan 2 mg

Arm description:

1 levosimendan 1 mg capsule in the morning and 1 mg capsule 12 hours later for 14 days.

Arm type	Experimental
Investigational medicinal product name	Levosimendan 1 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 levosimendan 1 mg capsule in the morning and 1 mg capsule 12 hours later for 14 days.

Arm title	Placebo

Arm description:

1 placebo capsule in the morning and 1 placebo capsule 12 hours later.

Arm type	Placebo

Investigational medicinal product name	Placebo levosimendan capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo levosimendan capsule containing only excipients.

Number of subjects in period 1	Levosimendan 1 mg	Levosimendan 2 mg	Placebo
Started	66	66	66
Completed	50	50	50
Not completed	16	16	16
Adverse event, serious fatal	1	1	1
Adverse event, non-fatal	7	7	7
Personal reason	3	3	3
Other	3	3	3
Adverse event, serious, non-fatal	2	2	2

Period 2

Period 2 title	Open label extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Opel label extension

Arm description:

Levosimendan treatment 1-2 mg was continued for 6 months.

Arm type	Experimental
Investigational medicinal product name	Levosimendan 1 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 mg dose of levosimendan in the morning for 2 weeks. Then the dose was increased to 1 mg b.i.d., if the 1 mg once a day dosing was well tolerated.

Number of subjects in period 2	Opel label extension
Started	50
Completed	35
Not completed	15
Adverse event, serious fatal	4
Adverse event, non-fatal	5
Personal reason	1
Other	2
Adverse event, serious, non-fatal	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Cross-over part

Reporting group description: -

Reporting group values	Cross-over part	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
Adults (18-64 years)	50	50	
Adults 65-84 years	16	16	
Gender categorical Units: Subjects			
Female	19	19	
Male	47	47	

End points

End points reporting groups

Reporting group title	Levosimendan 1 mg
Reporting group description:	
1 levosimendan 1 mg capsule in the morning and 1 placebo capsule 12 hours later for 14 days.	
Reporting group title	Levosimendan 2 mg
Reporting group description:	
1 levosimendan 1 mg capsule in the morning and 1 mg capsule 12 hours later for 14 days.	
Reporting group title	Placebo
Reporting group description:	
1 placebo capsule in the morning and 1 placebo capsule 12 hours later.	
Reporting group title	Opel label extension
Reporting group description:	
Levosimendan treatment 1-2 mg was continued for 6 months.	

Primary: SVC (sitting)

End point title	SVC (sitting)
End point description:	
The primary efficacy endpoint was SVC assessed in sitting position (% predicted for age, height and sex), defined as change from baseline at day 14 predose assessment.	
End point type	Primary
End point timeframe:	
Pre-dose on day 14	

End point values	Levosimendan 1 mg	Levosimendan 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	59	58	
Units: percent				
arithmetic mean (standard deviation)	-2.8 (± 8.9)	-1.9 (± 8.1)	-1.8 (± 7.3)	

Statistical analyses

Statistical analysis title	Change from baseline, SVC (sitting)
Statistical analysis description:	
Analysis of covariance	
Comparison groups	Levosimendan 1 mg v Placebo

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	ANCOVA

Statistical analysis title	Change from baseline, SVC (sitting)
Statistical analysis description: Analysis of covariance	
Comparison groups	Levosimendan 2 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	ANCOVA

Post-hoc: SVC (sitting, post-hoc)	
End point title	SVC (sitting, post-hoc)
End point description: Due to significant period effect, changes from period-wise baselines (period 1 day 1, period 2 day 1 and period 3 day 1, respectively) were considered as primary comparisons (post-hoc).	
End point type	Post-hoc
End point timeframe: Pre-dose on day 14	

End point values	Levosimendan 1 mg	Levosimendan 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	59	58	
Units: percent				
arithmetic mean (standard deviation)	-0.8 (± 7.1)	0.2 (± 7.3)	-0.7 (± 6.0)	

Statistical analyses

Statistical analysis title	Change from baseline SVC (sitting, post-hoc)
Comparison groups	Levosimendan 1 mg v Placebo

Number of subjects included in analysis	117
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.97
Method	ANCOVA

Statistical analysis title	Change from baseline SVC (sitting, post-hoc)
Comparison groups	Levosimendan 2 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.85
Method	ANCOVA

Post-hoc: SVC (supine, post-hoc)	
End point title	SVC (supine, post-hoc)
End point description:	
Due to significant period effect, changes from period-wise baselines (period 1 day 1, period 2 day 1 and period 3 day 1, respectively) were considered as primary comparisons (post-hoc).	
End point type	Post-hoc
End point timeframe:	
Pre-dose day 14	

End point values	Levosimendan 1 mg	Levosimendan 2 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	58	56	
Units: percent				
arithmetic mean (standard deviation)	1.0 (± 8.6)	2.7 (± 8.3)	-4.0 (± 9.4)	

Statistical analyses

Statistical analysis title	Change from baseline SVC (supine, post-hoc)
Comparison groups	Levosimendan 1 mg v Placebo
Number of subjects included in analysis	115
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.018
Method	ANCOVA

Statistical analysis title	Change from baseline SVC (supine, post-hoc)
Comparison groups	Levosimendan 2 mg v Placebo
Number of subjects included in analysis	114
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed from signing the informed consent until the end-of study visit. The duration of the study was about 13-14 weeks for the double-blind crossover part, and about 9-10 months for the entire study, including the 6 months open-label follow-up.

Adverse event reporting additional description:

Non-serious adverse events are reported, if the frequency in cross-over part was >/= 3 subjects, appr. 5 %.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Levosimendan 1 mg

Reporting group description:

1 levosimendan 1 mg capsule in the morning and 1 placebo capsule 12 hours later for 14 days.

Reporting group title	Levosimendan 2 mg

Reporting group description:

1 levosimendan 1 mg capsule in the morning and 1 mg capsule 12 hours later for 14 days.

Reporting group title	Placebo

Reporting group description:

1 placebo capsule in the morning and 1 placebo capsule 12 hours later.

Reporting group title	Open label extension

Reporting group description:

Levosimendan treatment 1-2 mg daily continued for 6 months

Serious adverse events	Levosimendan 1 mg	Levosimendan 2 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 59 (8.47%)	3 / 59 (5.08%)	6 / 58 (10.34%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	2 / 59 (3.39%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Respiratory failure			
subjects affected / exposed	1 / 59 (1.69%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nocturnal dyspnoea			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	0 / 58 (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
Muscular weakness			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	0 / 58 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open label extension		
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 50 (62.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Femoral neck fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pancreatic cyst			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders				
Respiratory failure				
subjects affected / exposed	6 / 50 (12.00%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Hypoventilation				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nocturnal dyspnoea				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Panic attack				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc protrusion				

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Levosimendan 1 mg	Levosimendan 2 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 59 (71.19%)	50 / 59 (84.75%)	31 / 58 (53.45%)
Investigations			
Heart rate increased			
subjects affected / exposed	1 / 59 (1.69%)	5 / 59 (8.47%)	0 / 58 (0.00%)
occurrences (all)	1	5	0
Oxygen saturation decreased			
subjects affected / exposed	3 / 59 (5.08%)	4 / 59 (6.78%)	0 / 58 (0.00%)
occurrences (all)	3	5	0
Blood glucose increased			

subjects affected / exposed	1 / 59 (1.69%)	3 / 59 (5.08%)	0 / 58 (0.00%)
occurrences (all)	1	3	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 59 (15.25%)	9 / 59 (15.25%)	5 / 58 (8.62%)
occurrences (all)	12	10	7
Skin abrasion			
subjects affected / exposed	3 / 59 (5.08%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	3
Contusion			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	2	3	2
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 59 (1.69%)	4 / 59 (6.78%)	0 / 58 (0.00%)
occurrences (all)	1	4	0
Tachycardia			
subjects affected / exposed	2 / 59 (3.39%)	2 / 59 (3.39%)	1 / 58 (1.72%)
occurrences (all)	2	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 59 (16.95%)	17 / 59 (28.81%)	2 / 58 (3.45%)
occurrences (all)	10	17	2
Dizziness			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 59 (6.78%)	1 / 59 (1.69%)	1 / 58 (1.72%)
occurrences (all)	4	1	1
Diarrhoea			
subjects affected / exposed	1 / 59 (1.69%)	3 / 59 (5.08%)	2 / 58 (3.45%)
occurrences (all)	1	3	2
Constipation			
subjects affected / exposed	2 / 59 (3.39%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	2	2	3

Abdominal pain upper			
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	1 / 58 (1.72%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 59 (10.17%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences (all)	6	0	1
Lower respiratory tract infection			
subjects affected / exposed	2 / 59 (3.39%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 59 (6.78%)	4 / 59 (6.78%)	3 / 58 (5.17%)
occurrences (all)	4	4	3

Non-serious adverse events	Open label extension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 50 (84.00%)		
Investigations			
Heart rate increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	14 / 50 (28.00%) 23		
Skin abrasion subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 1		
Contusion subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 10		
Tachycardia subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 6		
Dizziness subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Constipation subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Respiratory, thoracic and mediastinal			

disorders Cough subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 3 3 / 50 (6.00%) 4		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	 0 / 50 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 2 / 50 (4.00%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2015	Amendment 1.0. UK only. Addition and update to patient withdrawal criteria as requested by the UK CA. Superseded by Amendment 4.0
05 June 2015	Amendment 2.0. NL only. Addition and update to patient withdrawal criteria as requested by the UK CA. Superseded by Amendment 4.0.
16 July 2015	Amendment 3.0 Version 1.0. DE only. Superseded by Amendment 5. IC text updated. Acceptable forms of contraception added.
29 October 2015	Amendment 4.0. Version 1.0. Final protocol in countries listed: UK, NL only. • IC text updated • Subjects not taking riluzole allowed to enter the study • Changes to entry criteria to make them clinically more precise/adequate without affecting the scientific integrity of the study • Use of EMG in the diagnosis of ALS clarified
29 October 2015	Amendment 5.0 Version 1.0. Superseded by Amendment 5 Version 2. DE only. Inclusion of a DSMB for the study.
05 January 2016	Amendment 6.0 version 1.0 Not accepted by CA Superseded by AM6 version 2.0. IRE only. • IC text updated • Subjects not taking riluzole allowed to enter the study • Changes to entry criteria to make them clinically more precise/adequate without affecting the scientific integrity of the study • Use of EMG in the diagnosis of ALS clarified
04 March 2016	Amendment 6.0 version 2.0 Final protocol. IRE only. Update to study stopping rules regarding ventricular tachycardia.
22 April 2016	Amendment 5.0, Version 2.0 Final protocol. DE only. • IC text updated • Subjects not taking riluzole allowed to enter the study • Changes to entry criteria to make them clinically more precise/adequate without affecting the scientific integrity of the study • Use of EMG in the diagnosis of ALS clarified • Access to post study levosimendan updated • Order of assessment for respiratory and grip strength updated to be provided as separate instructions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported