

**Clinical trial results:**

Estudio multicéntrico de fase 3 de retirada aleatorizada, doble ciego y controlado con placebo, seguido de un periodo abierto de extensión para evaluar la eficacia y la seguridad del fosfato de amifampridina (fosfato de 3,4-diaminopiridina) en pacientes con el síndrome miasténico de Lambert-Eaton (LEMS)

A Phase 3, Multicenter, Double-blind, Placebo-controlled Randomized Discontinuation Study Followed by an Open-label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert-Eaton Myasthenic Syndrome (LEMS)

Summary

EudraCT number	2010-021850-20
Trial protocol	DE ES IT HU CZ BG
Global end of trial date	08 July 2016

Results information

Result version number	v1 (current)
This version publication date	21 October 2017
First version publication date	21 October 2017

Trial information**Trial identification**

Sponsor protocol code	LMS-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01377922
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Catalyst Pharmaceuticals, Inc.
Sponsor organisation address	335 Alhambra Circle, Suite 1250, Coral Gables, United States, 33134
Public contact	Head of Regulatory, Catalyst Pharmaceuticals, Inc., 1 305.420.3200, gingenito@catalystpharma.com
Scientific contact	Head of Regulatory, Catalyst Pharmaceuticals, Inc., 1 305.420.3200, gingenito@catalystpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	10 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study (LMS-002) was to evaluate the efficacy and safety, including the long-term efficacy (at least 91 days of previous amifampridine treatment) and safety (2-year, Open-label Long-term Safety), of amifampridine as a symptomatic treatment for patients with LEMS. This study was the first, randomized, placebo-controlled clinical efficacy study with amifampridine phosphate in patients with LEMS.

Protection of trial subjects:

Rescue treatment was provided to patients who experienced treatment failure as defined by meeting at least 1 of the following criteria: became non-ambulatory (after having been ambulatory at Screening), demonstrated an increase (worsening) in QMG score by >5 points, developed respiratory failure. Rescue Visit 1 and the confirmatory Rescue Visit 2 were performed as soon as a patient was identified as potentially requiring open-label amifampridine rescue treatment. Rescue treatment could include open-label amifampridine at a dose level determined by the investigator. Anti-tumor, immunologic, or symptomatic treatment for LEMS could be administered as determined by the investigator; however, immunosuppressives that lowered the seizure threshold (eg, cyclosporine, tacrolimus) or other aminopyridines were not permitted in combination with amifampridine.

Background therapy:

In addition to amifampridine, patients received best supportive care (BSC) treatment as determined by the investigator using concomitant medications permitted by protocol, which were as follows: (1) selected oral immunosuppressants (eg, prednisone or other corticosteroids; azathioprine, mycophenolate) and (2) peripherally acting cholinesterase inhibitors (eg, pyridostigmine).

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Czech Republic: 1

Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	54
EEA total number of subjects	15

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)	39
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 15 sites in 10 countries, including Argentina (1 site), Czech Republic (1 site), France (1 site), Germany (1 site), Hungary (1 site), Poland (1 site), Russia (1 site), Serbia (1 site), Spain (1 site), and the United States (6 sites).

Pre-assignment

Screening details:

After providing informed consent, patients underwent a screening evaluation to determine study eligibility. Efficacy and safety assessments were performed for all patients during screening. A total of 74 patients were screened and had data on the database. Twenty did not meet all eligibility criteria and were excluded from the study.

Pre-assignment period milestones

Number of subjects started	54
Intermediate milestone: Number of subjects	Amifampridine phosphate titration: 54
Intermediate milestone: Number of subjects	Minimum 91 days of amifampridine: 54
Number of subjects completed	38

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Directly go to Long-term Safety phase: 2
Reason: Number of subjects	Adverse event, non-fatal: 5
Reason: Number of subjects	Personal decision: 3
Reason: Number of subjects	Lack of efficacy: 2
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Intermittent heart block: 1
Reason: Number of subjects	Did not meet QMG criterion: 1
Reason: Number of subjects	Abnormal ECG: 1

Period 1

Period 1 title	Discontinuation-Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

A centralized randomization method (interactive voice/web response system [IXRS]) was used to assign one of the blinded treatments. For patients randomized to treatment discontinuation, blinding was maintained by providing patients with daily dose packets containing a constant number of tablets, which were a combination of placebo and amifampridine phosphate. The same investigator did not perform both the CMAP and QMG tests on an individual patient.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Continuation of Treatment
Arm description: Amifampridine phosphate at a dose established during the open-label pre-assignment phase was continued for a total of 14 days (7 day of the "discontinuation phase" plus 7 days of the "treatment phase").	
Arm type	Experimental
Investigational medicinal product name	Amifampridine phosphate
Investigational medicinal product code	
Other name	3,4-diaminopyridine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were required to be on a minimum of 30 mg/day of amifampridine to start the "discontinuation-treatment phase"; they had to continue the amifampridine treatment at least for 91 consecutive and have at least 7 consecutive days of stable open-label amifampridine dosing (ie, the same total daily dose and dose regimen) immediately before entering into "discontinuation-treatment phase". After randomization, amifampridine phosphate was continued for 7 days (at a dose established during Open-label pre-assignment period). All doses of study treatment were taken at home and with food.

Arm title	Discontinuation of Treatment
Arm description: The discontinuation of treatment involved downward titration of amifampridine phosphate dose to 0 mg beginning on Day 2 of the "discontinuation phase" by substituting an increasing proportion of matching placebo tablets. On Day 7 (end of the "discontinuation phase"), all tablets were placebo. Patients for whom the dose was titrated downward to placebo in the "discontinuation phase" remained on placebo for 7 days (Treatment phase).	
Arm type	Placebo
Investigational medicinal product name	Amifampridine phosphate
Investigational medicinal product code	
Other name	3,4-diaminopyridine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were required to be on a minimum of 30 mg/day of amifampridine to start the "discontinuation-treatment phase"; they had to continue the amifampridine treatment at least for 91 consecutive and have at least 7 consecutive days of stable open-label amifampridine dosing (ie, the same total daily dose and dose regimen) immediately before entering into "discontinuation-treatment phase". After randomization, amifampridine phosphate was continued for 7 days (at a dose established during Open-label pre-assignment period). All doses of study treatment were taken at home and with food.

Number of subjects in period 1^[1]	Continuation of Treatment	Discontinuation of Treatment
Started	16	22
Entry in the "Treatment phase"	16	21
Completed	16	21
Not completed	0	1
Rescue treatment required	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Sixteen patients did not successfully complete the pre-assignment period and were excluded from study prior to randomization.

Baseline characteristics

Reporting groups

Reporting group title	Continuation of Treatment
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Reporting group description:

Amifampridine phosphate at a dose established during the open-label pre-assignment phase was continued for a total of 14 days (7 day of the "discontinuation phase" plus 7 days of the "treatment phase").

Reporting group title	Discontinuation of Treatment
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Reporting group description:

The discontinuation of treatment involved downward titration of amifampridine phosphate dose to 0 mg beginning on Day 2 of the "discontinuation phase" by substituting an increasing proportion of matching placebo tablets. On Day 7 (end of the "discontinuation phase"), all tablets were placebo. Patients for whom the dose was titrated downward to placebo in the "discontinuation phase" remained on placebo for 7 days (Treatment phase).

Reporting group values	Continuation of Treatment	Discontinuation of Treatment	Total
Number of subjects	16	22	38
Age categorical Units: Subjects			
Adults (18-64 years)	13	18	31
From 65-84 years	3	3	6
85 years and over	0	1	1
Not recorded	0	0	0
Age continuous Units: years			
median	53	56.5	
full range (min-max)	25 to 67	21 to 88	-
Gender categorical Units: Subjects			
Female	9	14	23
Male	7	8	15
Not recorded	0	0	0
Number of patients taking amifampridine immediately prior to enrollment Units: Subjects			
Yes	3	7	10
No	13	15	28
Number of continuous days of amifampridine exposure prior to enrollment Units: days			
median	365	630	
full range (min-max)	365 to 5700	166 to 4457	-

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consisted of all randomized patients who received at least 1 dose of IP (amifampridine phosphate or placebo) in Part 2-discontinuation phase and who had at least one post baseline efficacy assessment. Patients were analyzed as randomized.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled patients (ie, entered in the open-label pre-assignment phase) who received at least 1 dose of study drug, and had any posttreatment safety information collected, were included in the safety analyses. Patients were analyzed as treated.

Subject analysis set title	Safety analysis Extension set
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients who had completed the pre-assignment period, discontinuation phase, and treatment phase; patients who had received rescue treatment with amifampridine phosphate during discontinuation and treatment phase; and patients participating in the pre-assignment period who had not had the opportunity to establish 7 days of stable amifampridine phosphate dosing could participate in the open-label, long term safety study. A total of 40 patients were enrolled into the open-label, long term safety study. This included all 38 patients, who participated in the discontinuation and treatment phases, and 2 patients who rolled over directly from the pre-assignment period.

Reporting group values	Full analysis set	Safety analysis set	Safety analysis Extension set
Number of subjects	38	53	40
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Not recorded			
Age continuous Units: years			
median	54.0	55	54.0
full range (min-max)	21 to 88	20 to 88	21 to 88
Gender categorical Units: Subjects			
Female	23	35	24
Male	15	18	16
Not recorded	0	0	0
Number of patients taking amifampridine immediately prior to enrollment Units: Subjects			
Yes			
No			
Number of continuous days of amifampridine exposure prior to enrollment Units: days			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	Continuation of Treatment
Reporting group description: Amifampridine phosphate at a dose established during the open-label pre-assignment phase was continued for a total of 14 days (7 day of the "discontinuation phase" plus 7 days of the "treatment phase").	
Reporting group title	Discontinuation of Treatment
Reporting group description: The discontinuation of treatment involved downward titration of amifampridine phosphate dose to 0 mg beginning on Day 2 of the "discontinuation phase" by substituting an increasing proportion of matching placebo tablets. On Day 7 (end of the "discontinuation phase"), all tablets were placebo. Patients for whom the dose was titrated downward to placebo in the "discontinuation phase" remained on placebo for 7 days (Treatment phase).	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set consisted of all randomized patients who received at least 1 dose of IP (amifampridine phosphate or placebo) in Part 2-discontinuation phase and who had at least one post baseline efficacy assessment. Patients were analyzed as randomized.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All enrolled patients (ie, entered in the open-label pre-assignment phase) who received at least 1 dose of study drug, and had any posttreatment safety information collected, were included in the safety analyses. Patients were analyzed as treated.	
Subject analysis set title	Safety analysis Extension set
Subject analysis set type	Safety analysis
Subject analysis set description: Patients who had completed the pre-assignment period, discontinuation phase, and treatment phase; patients who had received rescue treatment with amifampridine phosphate during discontinuation and treatment phase; and patients participating in the pre-assignment period who had not had the opportunity to establish 7 days of stable amifampridine phosphate dosing could participate in the open-label, long term safety study. A total of 40 patients were enrolled into the open-label, long term safety study. This included all 38 patients, who participated in the discontinuation and treatment phases, and 2 patients who rolled over directly from the pre-assignment period.	

Primary: Change in QMG score from baseline to Day 14

End point title	Change in QMG score from baseline to Day 14
End point description: The QMG is a physician-rated test including 13 assessments such as facial strength, swallowing, grip strength, and duration of time that limbs can be maintained in outstretched positions. The FDA accepted this endpoint along with SGI as coprimary endpoints, as part of its acceptance of the statistical analysis plan (SAP) for this study. A mixed-effect model repeated measures (MMRM) was used to analyze each component of the coprimary endpoint. The primary contrast was a comparison of the change from baseline in the QMG scores and SGI scores of those assigned to amifampridine phosphate to those assigned to placebo at Day 14. The treatment groups were compared at Day 14 using both QMG score and SGI score.	
End point type	Primary
End point timeframe: From day 1 to day 14	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: QMG score				
arithmetic mean (standard deviation)	0.3 (± 2.6)	2.2 (± 2.93)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline QMG score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Discontinuation of Treatment v Continuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0452 ^[1]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0

Notes:

[1] - The p-values was determined using a permutation test to estimate the effect of treatment on the mean differences in the primary efficacy endpoints (QMG and SGI scores) on Day 14 under strong test conditions.

Significant at 5% level.

Primary: Change in SGI score from baseline to Day 14

End point title	Change in SGI score from baseline to Day 14
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End point description:

The SGI is a 7-point scale on which the patients rated their global impression of the effects of the study treatment (1 = Terrible; 2 = Mostly Dissatisfied; 3 = Mixed; 4 = Partially Satisfied; 5 = Mostly Satisfied; 6 = Pleased; 7 = Delighted). The FDA accepted this endpoint along with QMG as coprimary endpoints, as part of its acceptance of the statistical analysis plan (SAP) for this study. A mixed-effect model repeated measures (MMRM) was used to analyze each component of the coprimary endpoint. The primary contrast was a comparison of the change from baseline in the QMG scores and SGI scores of those assigned to amifampridine phosphate to those assigned to placebo at Day 14. The treatment groups were compared at Day 14 using both QMG score and SGI score.

End point type	Primary
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End point timeframe:

From Day 1 to Day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: Score				
arithmetic mean (standard deviation)	-0.7 (± 1.82)	-2.7 (± 2.29)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline QMG score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028 ^[2]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	3

Notes:

[2] - The p-values was determined using a permutation test to estimate the effect of treatment on the mean differences in the primary efficacy endpoints (QMG and SGI scores) on Day 14 under strong test conditions.

Significant at 1% level.

Secondary: CGI-I Score at Day 14

End point title	CGI-I Score at Day 14
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End point description:

The CGI-I captured the investigator's global impression of improvement or worsening from baseline status. The 7-point scale was scored by the investigator (1 = Very much improved; 2 = Much improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse) based on changes in symptoms, behavior, and functional abilities. The CGI-I scale measurement on Day 14 was considered. CGI-I scale was analyzed by using a near identical mixed-model effects as used for the coprimary endpoints; however, there was no covariate for baseline value in the model.

End point type	Secondary
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End point timeframe:

Day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: score				
arithmetic mean (standard deviation)	3.6 (\pm 1.5)	4.8 (\pm 1.45)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0267 ^[3]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.1

Notes:

[3] - Pairwise contrast at Day 14 from MMRM model. Significant at 5%

Secondary: Change in T25FW walking speed from baseline to Day 14

End point title	Change in T25FW walking speed from baseline to Day 14
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End point description:

The T25FW test, a component of the Multiple Sclerosis Functional Composite, was a quantitative mobility and leg function performance test based on a timed 25-foot walk. The changes in the T25FW walking speed (feet/minute) from double-blind baseline (Part 2, Day 1) to Day 14 (end of Part 3) were analyzed using the same mixed-effects model used for the coprimary efficacy endpoints, but with double-blind baseline T25FW walking speed as the covariate.

End point type	Secondary
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End point timeframe:

From day 1 to day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: feet/minute				
arithmetic mean (standard deviation)	-1.46 (± 52.5)	-10.4 (± 53.1)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placeo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline T25FW walking speed as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6274 ^[4]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	8.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.77
upper limit	43.79

Notes:

[4] - Pairwise contrast at Day 14 from MMRM model.

Other pre-specified: Change in QMG Scores from baseline to Day 8

End point title	Change in QMG Scores from baseline to Day 8
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 8

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	0.1 (± 1.24)	3.6 (± 3.06)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description:	
LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline QMG score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Discontinuation of Treatment v Continuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-1.9

Notes:

[5] - Significant at 0.1% level

Other pre-specified: Change in QMG Scores for the Arms Subdomain from baseline to Day 8

End point title	Change in QMG Scores for the Arms Subdomain from baseline to Day 8
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	0 (± 0)	1.2 (± 1.15)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description: LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline QMG Subdomains Arms score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.6

Notes:

[6] - Pairwise contrast from MMRM model. Significant at 0.1% level.

Other pre-specified: Change in QMG Subdomain Arms Scores from Baseline to Day 14

End point title	Change in QMG Subdomain Arms Scores from Baseline to Day 14
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 14	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: score				
arithmetic mean (standard deviation)	0.3 (± 0.93)	0.9 (± 1.09)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Comparison groups	Continuation of Treatment v Discontinuation of Treatment

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0486 ^[7]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0

Notes:

[7] - Pairwise contrast from MMRM model. Significant at 5% level.

Other pre-specified: Change in QMG Subdomain Legs Scores from Baseline to Day 8

End point title	Change in QMG Subdomain Legs Scores from Baseline to Day 8
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	0.3 (± 0.68)	0.7 (± 1.35)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1508 ^[8]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.2

Notes:

[8] - Pairwise contrast from MMRM model

Other pre-specified: Change in QMG Subdomain Legs Scores from Baseline to Day 14

End point title	Change in QMG Subdomain Legs Scores from Baseline to Day 14
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: score				
arithmetic mean (standard deviation)	-0.1 (± 0.93)	0.6 (± 1.16)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0554 ^[9]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0

Notes:

[9] - Pairwise contrast from MMRM model

Other pre-specified: Change in CMAP Amplitude from Baseline to Day 8

End point title	Change in CMAP Amplitude from Baseline to Day 8
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 8

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: mV				
arithmetic mean (standard deviation)	0 (\pm 1.2)	-1.6 (\pm 1.82)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065 ^[10]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.6

Notes:

[10] - Pairwise contrast from MMRM model

Other pre-specified: Change in CMAP Amplitude from Baseline to Day 14

End point title	Change in CMAP Amplitude from Baseline to Day 14
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: mV				
arithmetic mean (standard deviation)	-0.7 (± 1.75)	-1 (± 2.2)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6398 ^[11]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.6

Notes:

[11] - Pairwise contrast from MMRM model

Other pre-specified: Percentage Change in CMAP Amplitude between First and Fifth CMAP in the First Series of 3 Hz Stimuli at Day 8

End point title	Percentage Change in CMAP Amplitude between First and Fifth CMAP in the First Series of 3 Hz Stimuli at Day 8
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End point description:

End point type	Other pre-specified
End point timeframe:	
From day 1 to day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: mV				
arithmetic mean (standard deviation)	-0.1 (± 6.53)	-4.5 (± 11.06)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description:	
LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1131 ^[12]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	11.1

Notes:

[12] - Pairwise contrast from MMRM model

Other pre-specified: Percentage Change in CMAP Amplitude between First and Fifth CMAP in the First Series of 3 Hz Stimuli at Day 14

End point title	Percentage Change in CMAP Amplitude between First and Fifth CMAP in the First Series of 3 Hz Stimuli at Day 14
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 14	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: mV				
arithmetic mean (standard deviation)	0.3 (± 10.43)	0.7 (± 52.42)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description: LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9928 ^[13]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.6
upper limit	26.8

Notes:

[13] - Pairwise contrast from MMRM model

Other pre-specified: Percentage Change in Amplitude Between First CMAP in the First Series of 3 Hz Stimuli and the Single CMAP Following Maximum Voluntary Contraction at Day 8

End point title	Percentage Change in Amplitude Between First CMAP in the First Series of 3 Hz Stimuli and the Single CMAP Following Maximum Voluntary Contraction at Day 8
End point description:	
End point type	Other pre-specified
End point timeframe: From day 1 to day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: mV				
arithmetic mean (standard deviation)	-4.3 (± 338.81)	82.4 (± 112.82)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the

dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7117 ^[14]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-187.5
upper limit	129.3

Notes:

[14] - Pairwise contrast from MMRM model

Other pre-specified: Percentage Change in Amplitude Between First CMAP in the First Series of 3 Hz Stimuli and the Single CMAP Following Maximum Voluntary Contraction at Day 14

End point title	Percentage Change in Amplitude Between First CMAP in the First Series of 3 Hz Stimuli and the Single CMAP Following Maximum Voluntary Contraction at Day 14
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 14	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: mV				
arithmetic mean (standard deviation)	-30.3 (± 402.2)	152.7 (± 377.05)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description:	
LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline value as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2923 ^[15]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-127.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-369.5
upper limit	114.5

Notes:

[15] - Pairwise contrast from MMRM model

Other pre-specified: CGI-I Scores at Day 8

End point title	CGI-I Scores at Day 8
End point description:	
End point type	Other pre-specified
End point timeframe:	
Day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	3.5 (± 0.97)	4.6 (± 1.53)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description:	
LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction as fixed effects and patient as a random effect. The model assumed time effect to be random between patients	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 ^[16]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.2

Notes:

[16] - Pairwise contrast at Day 8 from MMRM model

Other pre-specified: Change in SGI Scores from Baseline to Day 8

End point title	Change in SGI Scores from Baseline to Day 8
End point description:	
End point type	Other pre-specified
End point timeframe:	
From day 1 to day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	-0.3 (± 0.68)	-2.4 (± 2.24)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description:	
LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction and double-blind baseline SGI score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[17]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.1

Notes:

[17] - Pairwise contrast at Day 8 from MMRM model

Other pre-specified: Change in CGI-S Scores from Baseline to Day 8

End point title	Change in CGI-S Scores from Baseline to Day 8
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 8

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: score				
arithmetic mean (standard deviation)	-0.1 (± 0.25)	0.7 (± 1.32)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline CGI-S score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0537 ^[18]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0

Notes:

[18] - Pairwise contrast from MMRM model

Other pre-specified: Change in CGI-S Scores from Baseline to Day 14

End point title	Change in CGI-S Scores from Baseline to Day 14
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: score				
arithmetic mean (standard deviation)	0.2 (\pm 0.54)	1 (\pm 1.3)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline CGI-S score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075 ^[19]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.1

Notes:

[19] - Pairwise contrast from MMRM model

Other pre-specified: Change in T25FW walking speed from Baseline to Day 8

End point title	Change in T25FW walking speed from Baseline to Day 8
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End point description:

End point type	Other pre-specified
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End point timeframe:

From day 1 to day 8

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: feet/minute				
arithmetic mean (standard deviation)	7.96 (± 53.59)	-38.33 (± 72.55)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
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Statistical analysis description:

LS was estimated via a MMRM with change from baseline (Day 1, Part 2), Day 8, and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline T25FW Walking Speed as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0302 ^[20]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	47.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	89.92

Notes:

[20] - Pairwise contrast at Day 8 from MMRM model.

Other pre-specified: Change in CGI-I Scores from Baseline to Day 14

End point title	Change in CGI-I Scores from Baseline to Day 14
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End point description:

End point type	Other pre-specified
End point timeframe:	
From day 1 to day 14	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: score				
arithmetic mean (standard deviation)	1.1 (± 1.53)	2.2 (± 2.02)		

Statistical analyses

Statistical analysis title	Difference in LS means (amifampridine-placebo)
Statistical analysis description: LS was estimated via a MMRM with the scores at Day 8 and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline CGI-I score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.	
Comparison groups	Continuation of Treatment v Discontinuation of Treatment
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0252 ^[21]
Method	mixed-effects model repeated measures
Parameter estimate	Difference in LS means
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.1

Notes:

[21] - Pairwise contrast at Day 14 from MMRM model.

Other pre-specified: CGI-I Scale ratings of 1,2,3, and 4 at Day 8

End point title	CGI-I Scale ratings of 1,2,3, and 4 at Day 8
End point description:	
End point type	Other pre-specified
End point timeframe:	
Day 8	

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: Subject	16	10		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CGI-I Scale ratings of 1,2,3, and 4 at Day 14

End point title	CGI-I Scale ratings of 1,2,3, and 4 at Day 14
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End point description:

End point type	Other pre-specified
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End point timeframe:

Day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: Subject	13	14		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: SGI Scale Ratings of 4,5,6, or 7 at Day 8

End point title	SGI Scale Ratings of 4,5,6, or 7 at Day 8
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End point description:

The number reporting these high scores indicates patient happiness with treatment.

End point type	Other pre-specified
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End point timeframe:

Day 8

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: Subject	15	10		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: SGI Scale Ratings of 4,5,6, or 7 at Day 14

End point title	SGI Scale Ratings of 4,5,6, or 7 at Day 14
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End point description:

The number reporting these high scores indicates patient happiness with treatment.

End point type	Other pre-specified
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End point timeframe:

Day 14

End point values	Continuation of Treatment	Discontinuation of Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	21		
Units: Subject	12	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the pre-assignment period to the end of the "discontinuation-treatment phase" - from 12/09/2011 to 09/07/2014.

2-year Open-label extension phase lasted from 26/10/2011 to 08/07/2016

Adverse event reporting additional description:

Only treatment-emergent AEs (TEAEs) were included in the safety analysis.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	Pre-assignment period
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Reporting group description:

All enrolled patients entered in the open-label pre-assignment phase who received at least 1 dose of study drug, and had any posttreatment safety information collected, were included in the safety analyses.

Reporting group title	Discontinuation phase
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Reporting group description:

All patients randomized to continue amifampridine at the dosing established in the pre-assignment phase for 7 days or to downtitrate it to 0 mg in 7 days.

Reporting group title	Treatment phase
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Reporting group description:

Patients who continued amifampridine for 7 days and patients who had downtitrated amifampridine to 0 mg and received placebo for 7 days.

Reporting group title	Extension phase
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Reporting group description:

Patients who had completed the pre-assignment period, discontinuation phase, and treatment phase; patients who had received rescue treatment with amifampridine phosphate during discontinuation and treatment phase; and patients participating in the pre-assignment period who had not had the opportunity to establish 7 days of stable amifampridine phosphate dosing.

Serious adverse events	Pre-assignment period	Discontinuation phase	Treatment phase
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 53 (5.66%)	0 / 38 (0.00%)	0 / 38 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver enzymes elevation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Alanine aminotransferase increased			

subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant	Additional description: Microcellular pulmonic carcinoma		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Small cell lung cancer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Cardiac disorders			
Sick sinus syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Congestive cardiomyopathy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Sinus bradycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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			
Altered mental status			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Eye disorders			
Macular degeneration	Additional description: Worsening		

subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Glaucoma	Additional description: Left eye		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Cataract operation	Additional description: Right and left eye		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Gastroenteritis	Additional description: Acute		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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 / 53 (1.89%)	0 / 38 (0.00%)	0 / 38 (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
Embolism			
subjects affected / exposed	1 / 53 (1.89%)	0 / 38 (0.00%)	0 / 38 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 53 (1.89%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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			
Fracture	Additional description: Fractured hip due to fall		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
Weakness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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
LEMS	Additional description: Worsening of LEMS		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (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			
Viral infection	Additional description: Acute		
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 40 (25.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Liver enzymes elevation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant	Additional description: Microcellular pulmonic carcinoma		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Sick sinus syndrome			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congestive cardiomyopathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered mental status			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular degeneration	Additional description: Worsening		

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma	Additional description: Left eye		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract operation	Additional description: Right and left eye		
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis	Additional description: Acute		
subjects affected / exposed	1 / 40 (2.50%)		
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	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: Fractured hip due to fall		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weakness			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LEMS	Additional description: Worsening of LEMS		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection	Additional description: Acute		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pre-assignment period	Discontinuation phase	Treatment phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 53 (66.04%)	9 / 38 (23.68%)	9 / 38 (23.68%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Edema peripheral			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Pain			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Pyrexia			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 38 (2.63%) 1	0 / 38 (0.00%) 0
Seasonal allergy			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 38 (2.63%) 1	0 / 38 (0.00%) 0
Oropharyngeal pain			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 38 (2.63%) 1	0 / 38 (0.00%) 0
Chronic sinusitis			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 38 (2.63%) 1	0 / 38 (0.00%) 0
Dyspnea			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	1 / 38 (2.63%) 1
Investigations			
Creatinine Phosphokinase increased			
subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	1 / 38 (2.63%) 1
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 6	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Fall			
subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Cardiac disorders			

Cardiac disorder subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Nervous system disorders Nervous system disorder subjects affected / exposed occurrences (all)	23 / 53 (43.40%) 56	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	18 / 53 (33.96%) 36	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5	1 / 38 (2.63%) 2	0 / 38 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3	1 / 38 (2.63%) 1	0 / 38 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	1 / 38 (2.63%) 1
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Ear and labyrinth disorders Otitis externa subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	1 / 38 (2.63%) 1
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all) Paraesthesia oral	30 / 53 (56.60%) 62	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0

subjects affected / exposed	21 / 53 (39.62%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	23	0	0
diarrhoea			
subjects affected / exposed	5 / 53 (9.43%)	1 / 38 (2.63%)	0 / 38 (0.00%)
occurrences (all)	6	1	0
Nausea			
subjects affected / exposed	5 / 53 (9.43%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	5	0	0
Constipation			
subjects affected / exposed	3 / 53 (5.66%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	3	0	0
Hypoaesthesia oral			
subjects affected / exposed	3 / 53 (5.66%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 53 (0.00%)	2 / 38 (5.26%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Subcutaneous abscess			
subjects affected / exposed	0 / 53 (0.00%)	1 / 38 (2.63%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Renal and urinary disorders			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	8 / 53 (15.09%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	13	0	0
Pain in extremity			
subjects affected / exposed	3 / 53 (5.66%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	5	0	0
Muscular weakness			
subjects affected / exposed	0 / 53 (0.00%)	1 / 38 (2.63%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 38 (2.63%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Sensation of heaviness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Infections and infestations			
Infection			
subjects affected / exposed	11 / 53 (20.75%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	14	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 38 (0.00%)	1 / 38 (2.63%)
occurrences (all)	3	0	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 53 (5.66%)	1 / 38 (2.63%)	0 / 38 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 38 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Extension phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 40 (62.50%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Edema peripheral			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Chronic sinusitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dyspnea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Investigations			
Creatinine Phosphokinase increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		

Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	7		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Otitis externa			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Eye disorders			

Ocular hyperaemia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Gastrointestinal disorders			
Gastrointestinal disorder subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
diarrhoea subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Hypoaesthesia oral subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Erythema subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Subcutaneous abscess subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Periodontitis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Pulpitis dental subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Rash			

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Renal and urinary disorders subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Musculoskeletal and connective tissue disorders Musculoskeletal disorder subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Muscular weakness subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Myalgia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Asthenia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Sensation of heaviness subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Infections and infestations Infection subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		

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