

**Clinical trial results:**

A phase 3, multicenter, double-blind, placebo-controlled, randomized, outpatient two-period two-treatment crossover study to evaluate the efficacy and safety of amifampridine phosphate (3,4 diaminopyridine phosphate) in patients with Congenital Myasthenic Syndromes (CMS)

Summary

EudraCT number	2018-000358-23
Trial protocol	IT
Global end of trial date	24 January 2019

Results information

Result version number	v1 (current)
This version publication date	03 May 2021
First version publication date	03 May 2021

Trial information**Trial identification**

Sponsor protocol code	CMS-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02562066
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 106263

Notes:

Sponsors

Sponsor organisation name	Catalyst Pharmaceuticals Inc.
Sponsor organisation address	355 Alhambra Circle, Coral Gables, United States, 33134
Public contact	Gary Ingenito, Catalyst Pharmaceuticals Inc., 001 (305) 420-3200, gingenito@catalystpharma.com
Scientific contact	Gary Ingenito, Catalyst Pharmaceuticals Inc., 001 (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 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	13 January 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with CMS;
- To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with CMS, based on improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores

Protection of trial subjects:

The investigator could prescribe additional medications during the study, as long as the prescribed medication was not prohibited by the protocol. In the event of an emergency, any needed medications could be prescribed without prior approval, but it was required that the Medical Monitor be notified of the use of any contraindicated medications immediately thereafter.

Background therapy:

None

Evidence for comparator:

The diagnosis and management of children with congenital myasthenic syndromes (CMS) are challenging and the response to treatment in CMS depends on the type of defect (pre-synaptic, synaptic, post-synaptic) and the kinetics of the channel affected (fast versus slow). Most patients are eligible and respond to pharmacologic intervention, including acetylcholinesterase inhibitors, 3,4-diaminopyridine (3,4-DAP), ephedrine, fluoxetine or quinidine, and albuterol. The particular therapy is dictated by the diagnosed CMS subtype, as drugs beneficial in one subtype can be detrimental in another subtype.

Actual start date of recruitment	30 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	16
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	9
Adolescents (12-17 years)	3
Adults (18-64 years)	3
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 08 February 2016 to 24 January 2019, at 6 sites in the US and one site in Canada, patients were recruited and, after screening, were randomized on the last day of the open-label run-in period (Day 0) to either Treatment Sequence 1 or 2, in a 1:1 ratio.

Pre-assignment

Screening details:

Patients who completed screening proceeded to the run-in period. Patients who were previously naïve to amifampridine or amifampridine phosphate treatment began up-titration of medication, with frequent clinic evaluation for up to 4 weeks, until reaching a stable dose and frequency for 7 days. The patient must improve by 20% on MFM20 or 32.

Pre-assignment period milestones

Number of subjects started	27 ^[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 11
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Notes:

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

Justification: Some patients who had started the pre-assignment period were screen failures and were not enrolled in the trial.

Period 1

Period 1 title	Period 1 Days 1-8
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

The placebo was provided as tablets indistinguishable from amifampridine phosphate.

Arms

Are arms mutually exclusive?	Yes
Arm title	Amifampridine phosphate
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Amifampridine phosphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The amifampridine phosphate total daily dose of 10 mg to 80 mg, given in 2 to 4 divided doses, with no single dose >15 mg in patients up to 16 years of age or >20 mg in patients >16 years of age was chosen based on completed animal and in vitro pharmacology, pharmacokinetic, and toxicology studies. The dose of amifampridine phosphate was individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day. Doses of amifampridine phosphate were taken with food (e.g., breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit.

Arm title	Placebo
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Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A placebo equivalent was provided as tablets indistinguishable from the amifampridine phosphate tablets. The placebo was administered consistent with the dosing regimen of amifampridine phosphate. The dose of amifampridine phosphate was individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day. Doses of amifampridine phosphate were taken with food (e.g., breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit.

Number of subjects in period 1	Amifampridine phosphate	Placebo
Started	8	8
Completed	8	7
Not completed	0	1
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Period 2 Days 21-29
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Amifampridine phosphate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Amifampridine phosphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The amifampridine phosphate total daily dose of 10 mg to 80 mg, given in 2 to 4 divided doses, with no single dose >15 mg in patients up to 16 years of age or >20 mg in patients >16 years of age was chosen based on completed animal and in vitro pharmacology, pharmacokinetic, and toxicology studies. The dose of amifampridine phosphate was individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day. Doses of amifampridine phosphate were taken with food (e.g., breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A placebo equivalent was provided as tablets indistinguishable from the amifampridine phosphate tablets. The placebo was administered consistent with the dosing regimen of amifampridine phosphate. The dose of amifampridine phosphate was individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day. Doses of amifampridine phosphate were taken with food (e.g., breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit.

Number of subjects in period 2	Amifampridine phosphate	Placebo
Started	7	8
Completed	7	7
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Amifampridine phosphate
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Amifampridine phosphate	Placebo	Total
Number of subjects	8	8	16
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	12.56	27.35	-
standard deviation	± 15.70	± 25.00	-
Gender categorical Units: Subjects			
Female	5	3	8
Male	3	5	8
Mutations Units: Subjects			
Pre-synaptic mutation	2	0	2
Post-synaptic mutation	6	8	14
Race Units: Subjects			
White	8	5	13
Black or African America	0	1	1
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	2	2
Decline/refuse to answer	0	0	0
Weight Units: Kg			
arithmetic mean	27.81	54.00	-
standard deviation	± 11.15	± 28.22	-

SGI Score Day 0			
The SGI was a 7-point scale on which the patient rated their global impression of the effects of a study treatment (1=terrible to 7=delightful). The SGI was assessed by the patient or the patient's parent/guardian/caregiver if the patient was unable to complete the SGI. The SGI had demonstrated concordance with the physician's assessment of improvement.			
Units: Score			
arithmetic mean	5.11	5.75	
standard deviation	± 1.45	± 1.04	-
SGI Score Day 21			
The SGI was a 7-point scale on which the patient rated their global impression of the effects of a study treatment (1=terrible to 7=delightful). The SGI was assessed by the patient or the patient's parent/guardian/caregiver if the patient was unable to complete the SGI. The SGI had demonstrated concordance with the physician's assessment of improvement.			
Units: Score			
arithmetic mean	5.88	6.14	
standard deviation	± 0.64	± 1.21	-
Slurp test Day 0			
The slurp test was optional. Subjects were instructed to drink four ounces of water through a standard flex straw as quickly as possible, making a loud slurping sound at the end. The duration of time from the start of drinking the water to the slurp sound was recorded. On Day 0 this test was performed by 2 subjects in the group of amifampridine and 3 subjects in the placebo group.			
Units: second			
arithmetic mean	12.95	7.73	
standard deviation	± 5.59	± 2.88	-
Slurp test Day 21			
The slurp test was optional. Subjects were instructed to drink four ounces of water through a standard flex straw as quickly as possible, making a loud slurping sound at the end. The duration of time from the start of drinking the water to the slurp sound was recorded. On Day 21 this test was performed by 6 subjects in the group of amifampridine and 4 subjects in the placebo group.			
Units: second			
arithmetic mean	13.64	8.33	
standard deviation	± 10.73	± 1.83	-

End points

End points reporting groups

Reporting group title	Amifampridine phosphate
Reporting group description:	-
Reporting group title	Placebo
Reporting group description:	-
Reporting group title	Amifampridine phosphate
Reporting group description:	-
Reporting group title	Placebo
Reporting group description:	-

Primary: Change from baseline SGI score

End point title	Change from baseline SGI score
End point description:	The SGI allowed patients to rate the impression of the effects of study medication on their physical wellbeing during the preceding week using a 7-point scale. In studies of patients with chronic pain, a reduction of approximately two points represented a clinically important difference.
End point type	Primary
End point timeframe:	On Day 0 (baseline), day 8, day 21 (baseline) day 29.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	7	8
Units: Score				
arithmetic mean (standard deviation)	-0.13 (± 1.81)	-1.75 (± 2.12)	-1.14 (± 1.68)	-0.75 (± 1.75)

Statistical analyses

Statistical analysis title	Change from baseline at the end of period 1
Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.085 ^[1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - A Mann-Whitney-Wilcoxon test demonstrated that the difference in mean CFB in SGI score at the end of Study Period 1 was not statistically significant (p=0.085) between the two sequences.

Statistical analysis title	Change from baseline crossover
Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
P-value	= 0.441
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - The difference between the Period 1 CFB and Period 2 CFB was analyzed in the Mann-Whitney-Wilcoxon test. The results demonstrate that while subjects may have experienced an improvement in raw SGI scores while taking amifampridine phosphate versus placebo the treatment effect was not statistically significant.

Secondary: Change from baseline MFM-20 score

End point title	Change from baseline MFM-20 score
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End point description:

D-1, Standing Position and Transfers; D-2, Axial and Proximal Limb Motor Function; and D-3, Distal Motor Function.

The MFM was not the best scale for measuring symptoms and individual patient deficits. Particularly, in patients who had oculo-bulbar deficits (e.g., difficulty swallowing and respiratory deficits) the MFM is focused on motor movements and, as such, these patients may not have demonstrated improvement on the MFM scale. Nevertheless, the MFM was the only validated scale to include children as young as 2 years old and was therefore chosen for measurement of the secondary efficacy endpoint in this first placebo-controlled trial of genetically confirmed CMS patients.

End point type	Secondary
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End point timeframe:

Day 8 and Day 29

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	2
Units: Score				
arithmetic mean (standard deviation)				
Total	-1.50 (± 4.20)	-0.50 (± 6.36)	1.50 (± 2.12)	-0.75 (± 0.50)
D-1	-1.00 (± 2.58)	1.00 (± 4.24)	1.00 (± 4.24)	-1.75 (± 0.96)
D-2	0.25 (± 0.50)	-1.50 (± 2.12)	0.00 (± 0.00)	0.25 (± 0.50)
D-3	-0.75 (± 1.50)	0.00 (± 0.00)	0.50 (± 0.71)	0.75 (± 0.96)

Statistical analyses

Statistical analysis title	Change from baseline
Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - A Mann-Whitney-Wilcoxon test demonstrated that the difference in mean CFB in MFM-20 score at the end of Study Period 1 was not statistically significant (p=0.800) between the two sequences.

Statistical analysis title	Change from baseline crossover
Statistical analysis description: A Mann-Whitney-Wilcoxon test compared the difference between the Period 1 CFB and Period 2 CFB. were not statistically significant for any of the three dimensions (D-1, Standing Position and Transfers; D-2, Axial and Proximal Limb Motor Function; and D-3, Distal Motor Function). Therefore, while subjects may have experienced an improvement in raw MFM-20 scores while taking amifampridine phosphate versus placebo, the treatment effect was not statistically significant.	
Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.933
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline MFM-32 score

End point title	Change from baseline MFM-32 score
End point description: D-1, Standing Position and Transfers; D-2, Axial and Proximal Limb Motor Function; and D-3, Distal Motor Function	
End point type	Secondary
End point timeframe: Day 8 and day 29	

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	5	4
Units: Score				
arithmetic mean (standard deviation)				
Total	3.00 (± 3.92)	-0.17 (± 4.58)	-0.60 (± 0.89)	0.75 (± 2.22)
D-1	0.00 (± 1.83)	-0.67 (± 4.37)	0.20 (± 1.10)	0.50 (± 1.83)
D-2	0.75 (± 0.96)	0.33 (± 0.82)	-0.20 (± 0.45)	0.00 (± 0.00)
D-3	2.25 (± 1.26)	0.17 (± 0.41)	-0.60 (± 0.89)	0.25 (± 1.71)

Statistical analyses

Statistical analysis title	Change from baseline
Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.376 ^[4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - A Mann-Whitney-Wilcoxon test demonstrated that the difference in mean CFB in MFM-32 total score at the end of Study Period 1 was not statistically significant ($p=0.376$) between sequences.

Statistical analysis title	Change from baseline crossover
Statistical analysis description: A Mann-Whitney-Wilcoxon test compared the difference between the Period 1 CFB and Period 2 CFB. There were no statistically significant differences for dimensions 1 or 2 but were statistically significant for Period 1 of dimension 3 ($p=0.010$). These results demonstrate that subjects experienced a treatment benefit in regard to dimension 3 (distal motor function) while continuing amifampridine phosphate.	
Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.452
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical Global Impression – Severity Day 8

End point title	Clinical Global Impression – Severity Day 8
End point description:	
End point type	Secondary
End point timeframe: From baseline to Day 8	

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: subject				
1 normal, not ill at all	0	1		
2 borderline mentally ill	3	3		
3 mildly ill	3	1		
4 moderately ill	2	1		

Attachments (see zip file)	Clinical Global Impression.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression – Severity Day 29

End point title	Clinical Global Impression – Severity Day 29
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End point description:

End point type Secondary

End point timeframe:

From Day 21 to Day 29

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: subject				
1 normal, not at all ill	1	2		
2 borderline mentally ill	1	2		
3 mildly ill	4	3		
4 moderately ill	1	1		

Attachments (see zip file) Clinical Global Impression.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression - Improvement Day 8

End point title Clinical Global Impression - Improvement Day 8

End point description:

End point type Secondary

End point timeframe:

From baseline to Day 8

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: subject				
1 very much improved	0	0		
2 much improved	1	1		
3 minimally improved	2	1		
4 no change	4	3		
5 minimally worse	1	1		
6 much worse	0	1		
7 very much worse	0	0		

Attachments (see zip file)	Clinical Global Impression Improvement.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression - Improvement Day 29

End point title	Clinical Global Impression - Improvement Day 29
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End point description:

End point type	Secondary
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End point timeframe:

From Day 21 to Day 29

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: subject				
1 very much improved	0	1		
2 much improved	2	1		
3 minimally improved	3	4		
4 no change	2	0		
5 minimally worse	0	0		
6 much worse	0	0		
7 very much worse	0	0		

Attachments (see zip file)	Clinical Global Impression Improvement.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Slurp Test Day 8

End point title	Slurp Test Day 8
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End point description:

End point type	Secondary
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End point timeframe:
From baseline to Day 8

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: second				
arithmetic mean (standard deviation)	2.25 (\pm 1.07)	-0.40 (\pm 2.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Slurp Test Day 29

End point title | Slurp Test Day 29

End point description:

End point type | Secondary

End point timeframe:
From Day 21 to Day 29

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: second				
arithmetic mean (standard deviation)	-0.48 (\pm 1.72)	-2.66 (\pm 9.04)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent signature to through the last visit (Study Day 29) or at the early termination visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety population
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Reporting group description:

The safety population consisted of all randomized patients who received at least one dose of study medication.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Food poisoning subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Paraesthesia oral subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Retching subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3		
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Anger	1 / 16 (6.25%) 1		

<p>subjects affected / exposed occurrences (all)</p> <p>Irritability subjects affected / exposed occurrences (all)</p>	<p>1 / 16 (6.25%) 1</p> <p>1 / 16 (6.25%) 1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Pain in extremity subjects affected / exposed occurrences (all)</p> <p>Hypoaesthesia subjects affected / exposed occurrences (all)</p> <p>Migraine subjects affected / exposed occurrences (all)</p> <p>Paraesthesia subjects affected / exposed occurrences (all)</p>	<p>1 / 16 (6.25%) 1</p> <p>1 / 16 (6.25%) 1</p> <p>1 / 16 (6.25%) 1</p> <p>2 / 16 (12.50%) 2</p>		
<p>Infections and infestations</p> <p>Conjunctivitis subjects affected / exposed occurrences (all)</p> <p>Nasopharyngitis subjects affected / exposed occurrences (all)</p> <p>Parainfluenzae virus subjects affected / exposed occurrences (all)</p> <p>Rhinovirus infection subjects affected / exposed occurrences (all)</p> <p>Upper respiratory tract infection subjects affected / exposed occurrences (all)</p>	<p>1 / 16 (6.25%) 1</p> <p>3 / 16 (18.75%) 3</p> <p>1 / 16 (6.25%) 1</p> <p>1 / 16 (6.25%) 1</p> <p>2 / 16 (12.50%) 2</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	Administrative change to clarify the original intent of a reasonable time (at least three months) between the last SGI and MFM 20 or MFM 30 assessments and the first incidence of these assessments in the protocol. This was done to provide clarity on duration between testing to avoid testing bias.
07 March 2016	An administrative change to correct the use of the term "sequence" from "period" and "outpatient" versus "office visit". This was done to provide clarity.
25 April 2017	This amendment increased the age range of eligible subjects, expanded the statistical analysis section of the protocol increased the number of patients in the study from 10 to 23 and updated previous instruction language regarding dosing on the days of clinic evaluations.
26 June 2017	Amendments 4 and 5 formally removed videotaping of patients from the protocol, clarified start and stop times of Periods 1 and 2, blinded medication dosing, and removed the Day 36 visit. The patient was either on a stable dose of amifampridine phosphate or had been titrated over a period of 4 weeks. Additionally, the patient was observed on open-label medication for 2 weeks during the restabilization period. Therefore, the Day 36 visit on open-label medication provided no new information to the efficacy or safety profile of amifampridine phosphate and the patient could then go directly into the expanded access program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: