Clinical trial results:
A Randomized, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Amifampridine Phosphate in Ambulatory Patients with Spinal Muscular Atrophy (SMA) Type 3

Summary

EudraCT number	2017-004600-22
Trial protocol	IT
Global end of trial date	17 September 2020

Results information

Result version number	v1 (current)
This version publication date	06 May 2021
First version publication date	06 May 2021

Trial information

Trial identification

Sponsor protocol code	SMA-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Catalyst Pharmaceuticals Inc.
Sponsor organisation address	355 Alhambra Circle, Suite 1250, Coral Gables, United States, 33134
Public contact	Gary Ingenito, Catalyst Pharmaceuticals, Inc, +1 3054203200, gingenito@catalystpharma.com
Scientific contact	Gary Ingenito, Catalyst Pharmaceuticals, Inc, +1 3054203200, 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	10 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2020
Was the trial ended prematurely?	No

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 SMA Type 3.
To assess the clinical efficacy of amifampridine phosphate compared with placebo in ambulatory patients with SMA Type 3 using the Hammersmith Functional Motor Scale Expanded (HFMSE).

Protection of trial subjects:

Patients with concomitant use of medicinal products with a known potential to cause QTc prolongation and patients with long QT syndromes were no longer excluded. Exclusions for patients with uncontrolled asthma, concomitant use with sultopride, and concomitant use with medicinal products with a narrow therapeutic window were added. Additional contraindicated concomitant medications were also added including medicinal products with a narrow therapeutic window and sultopride. Caution when taking amifampridine with the following concomitant medications was added: medicinal products known to lower the epileptic threshold, medicinal products with atropine effects, medicinal products with cholinergic effects, non-depolarizing muscle relaxant acting medicinal products, and depolarizing muscle relaxant acting medicinal products.

Background therapy:

None

Evidence for comparator:

Not reported

Actual start date of recruitment	15 March 2018
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	Italy: 6
Country: Number of subjects enrolled	Serbia: 7
Worldwide total number of subjects	13
EEA total number of subjects	6

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)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 14 January 2019 to 17 September 2020, 13 SMA Type 3 ambulatory patients were recruited in Italy and Serbia.

Pre-assignment

Screening details:

Patients were screened for eligibility and those who had procedures/assessments completed during Run-in, until an optimized stable dose and frequency of amifampridine phosphate was established. At the end of seven days on a stable daily regimen, the patient was required to show ≥ a 3-point improvement in HFMSE score to be randomized.

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 1

Period 1

Period 1 title	Period 1 Week 1-2
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Amifampridine phosphate

Arm description: -

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

Dosage and administration details:

10 mg

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:

10 mg, as the experimental product

Number of subjects in period 1[1]	Amifampridine phosphate	Placebo
Started	6	6
Completed	6	6

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: The worldwide number consists of all patients enrolled; one of them has not been randomized and, therefore, is not included in the study groups.

Period 2

Period 2 title	Period 2 Week 3-4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Amifampridine phosphate

Arm description: -

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

Dosage and administration details:

10 mg

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

10 mg, as the experimental product

Number of subjects in period 2	Amifampridine phosphate	Placebo
Started	6	6
Completed	6	6

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	6	6	12
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	37.2	30.2	
standard deviation	± 8.5	± 13.5	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	2	5	7
Ethnicity Units: Subjects			
Caucasian	6	5	11
Black	0	0	0
Asian	0	1	1
Other	0	0	0
Height Units: cm			
arithmetic mean	169.3	174.8	
standard deviation	± 9.0	± 6.1	-
Weight Units: Kg			
arithmetic mean	64.7	67.8	
standard deviation	± 9.3	± 11.8	-
Body Mass Index Units: Kg/m2			
arithmetic mean	22.5	22.3	
standard deviation	± 1.4	± 4.3	-

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 HFMSE score	
End point title	Change from baseline HFMSE score
End point description:	
End point type	Primary
End point timeframe:	
The change in the HFMSE score was measured at baseline and after two weeks of treatment, in each period.	

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: score				
arithmetic mean (standard deviation)	0.333 (± 0.816)	-0.833 (± 1.722)	0.667 (± 1.366)	-0.333 (± 1.506)

Statistical analyses

Statistical analysis title	Change from baseline Overall
Statistical analysis description:	
The LS Means, p-value, and 95% CI were obtained using a 2-period 2- treatment crossover model through Day 28.	
Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0083 [1]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	0.792

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.37

Notes:

[1] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.
P-value period 0.9449
P-value Carry-over 0.1931

Secondary: CFB in 6-minute Walk Test

End point title	CFB in 6-minute Walk Test

End point description:

End point type	Secondary

End point timeframe:

The change in the 6-minute Walk Test was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: meter				
arithmetic mean (standard deviation)	1.500 (± 55.945)	0.833 (± 9.283)	15.000 (± 19.055)	12.333 (± 39.603)

Statistical analyses

Statistical analysis title	Change from baseline Overall

Statistical analysis description:

The LS Means, p-value, and 95% CI were obtained using a 2-period 2-treatment crossover model through Day 28.

Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [2]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.25
upper limit	10.25

Notes:

[2] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.
P-value Period 0.9260
P-value Carry-over 0.0682

Secondary: CFB in Rising from Floor

End point title	CFB in Rising from Floor

End point description:

End point type	Secondary

End point timeframe:

The change in the Rising from floor test was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	2	2
Units: second				
arithmetic mean (standard deviation)	7.420 (± 5.063)	11.000 (± 4.000)	10.500 (± 3.536)	6.500 (± 3.536)

Statistical analyses

Statistical analysis title	Change from baseline Overall

Statistical analysis description:

The LS Means, p-value, and 95% CI were obtained using a 2-period 2-treatment crossover model through Day 28.

Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.415 [3]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	-1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.48
upper limit	2.86

Notes:

[3] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.

Secondary: CFB in Rising from a Chair

End point title	CFB in Rising from a Chair

End point description:

End point type	Secondary

End point timeframe:

The change in the rising from a chair test was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	5
Units: second				
arithmetic mean (standard deviation)	-1.296 (± 2.224)	-0.040 (± 0.069)	-0.140 (± 0.242)	-0.738 (± 2.928)

Statistical analyses

Statistical analysis title	Change from baseline Overall
Comparison groups	Placebo v Amifampridine phosphate v Amifampridine phosphate v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.4548 [5]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	-0.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	0.63

Notes:

[4] - The LS Means, p-value, and 95% CI were obtained using a 2-period 2-treatment crossover model through Day 28.

[5] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.
P-value period: 0.4422
P-value carry-over: 0.9336

Secondary: CFB in Climbing 4 Steps

End point title	CFB in Climbing 4 Steps

End point description:

End point type	Secondary

End point timeframe:

The change in the climbing 4 steps test was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	3	6
Units: second				
arithmetic mean (standard deviation)	-1.122 (± 0.743)	0.127 (± 0.155)	0.000 (± 0.000)	-3.403 (± 6.019)

Statistical analyses

Statistical analysis title	Change from baseline Overall
Comparison groups	Amifampridine phosphate v Placebo v Amifampridine phosphate v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.4908 [7]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	0.479
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	1.89

Notes:

[6] - The LS Means, p-value, and 95% CI were obtained using a 2-period 2-treatment crossover model through Day 28.
[7] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.

Secondary: CFB in Walking 10 Meters

End point title	CFB in Walking 10 Meters

End point description:

End point type	Secondary

End point timeframe:

The change in the Walking 10 meters test was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: second				
arithmetic mean (standard deviation)	-0.667 (± 0.387)	-1.225 (± 1.874)	-5.382 (± 12.555)	-0.690 (± 0.531)

Statistical analyses

Statistical analysis title	Change from baseline Overall
Comparison groups	Placebo v Amifampridine phosphate v Amifampridine phosphate v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0867 [8]
Method	Crossover model
Parameter estimate	Mean difference (final values)
Point estimate	-1.803
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	0.27

Notes:

[8] - P-value (Period) and P-value (Carry-over) are the p-values for the corresponding effects in the model.

Secondary: CFB in the INQOL Subscales Scores

End point title	CFB in the INQOL Subscales Scores

End point description:

The change from baseline is reported for each item.

End point type	Secondary

End point timeframe:

The change in the INQOL score was measured at baseline and after two weeks of treatment, in each period.

End point values	Amifampridine phosphate	Placebo	Amifampridine phosphate	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: score				
arithmetic mean (standard deviation)				
Weakness score	2.632 (± 18.459)	-1.754 (± 13.175)	-7.018 (± 10.872)	0.877 (± 20.632)
Pain score	-2.632 (± 28.586)	-0.877 (± 5.175)	0.000 (± 0.000)	2.632 (± 30.463)

Fatigue score	0.000 (± 24.686)	2.632 (± 18.156)	-9.649 (± 25.442)	5.263 (± 6.657)
Muscle locking score	-7.018 (± 17.189)	0.000 (± 9.986)	-4.386 (± 16.448)	-5.263 (± 18.533)
Droopy eyelids score	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)
Double vision score	-5.263 (± 12.892)	0.000 (± 0.000)	0.000 (± 0.000)	-5.263 (± 12.892)
Swallowing difficulties score	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)	0.000 (± 0.000)
Activities score	-5.556 (± 11.142)	-12.654 (± 22.150)	-19.907 (± 18.525)	-7.562 (± 11.164)
Independence score	-2.778 (± 10.541)	-1.852 (± 17.003)	-9.259 (± 18.481)	-1.852 (± 17.003)
Social relationship score	3.395 (± 9.563)	-5.093 (± 9.049)	-3.549 (± 8.966)	2.623 (± 9.719)
Emotions score	0.000 (± 15.516)	1.389 (± 11.752)	1.389 (± 7.607)	-5.556 (± 17.830)
Body image score	0.000 (± 9.129)	-8.796 (± 12.097)	-8.333 (± 17.830)	-0.463 (± 20.126)
Perceived treatment effects score	-8.333 (± 24.721)	-8.333 (± 21.082)	-12.500 (± 25.685)	-2.778 (± 20.861)
Expected treatment effects score	-16.667 (± 23.570)	-6.944 (± 17.808)	-12.500 (± 20.242)	-6.944 (± 14.353)
Quality of life score	7.593 (± 13.299)	-3.611 (± 5.630)	-3.704 (± 11.367)	8.796 (± 15.008)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the enrolment to the end of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	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 / 12 (100.00%)		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Gastrointestinal disorders Paraesthesia oral subjects affected / exposed occurrences (all) Hypoaesthesia oral subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3 1 / 12 (8.33%) 1		
Respiratory, thoracic and mediastinal disorders Intranasal paraesthesia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

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