Clinical trial results:
A Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Amifampridine Phosphate in Patients with MuSK Antibody Positive Myasthenia Gravis, and a Sample of AChR Antibody Positive Myasthenia Gravis Patients

Summary

EudraCT number	2017-004018-25
Trial protocol	IT
Global end of trial date	24 April 2020

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	MSK-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03304054
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., 001 3054203200, gingenito@catalystpharma.com
Scientific contact	Gary Ingenito, Catalyst Pharmaceuticals Inc., 001 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	17 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 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 MuSK antibody positive myasthenia gravis.
To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with MuSK antibody positive myasthenia gravis based on change in Myasthenia Gravis Activities of Daily Living Score (MG-ADL)

Protection of trial subjects:

In the event of an emergency, any needed medications could be prescribed without prior approval, however, the medical monitor was notified of the use of any contraindicated medications immediately thereafter.
The measures of safety used in this study were routine clinical and laboratory procedures. The efficacy measures used a variety of approaches to evaluate changes in neuromuscular function and muscle strength. These standardized tests have been previously used for the determination of response to therapeutic intervention in patients with MG and in other indications and, thus, were relevant for use in this study in patients with MG.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	01 June 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: 27
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	89
EEA total number of subjects	27

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)	74
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment started on 1 June 2018, in 26 sites in the USA and Europe (Italy and Serbia). Approximately 60 male and female MuSK-MG subjects and 10 AChR-MG subjects were planned to be recruited.

Pre-assignment

Screening details:

After signing the informed consent, patients were screened and conducted at the start of the Run-in period. During the Run-in a stable dose and frequency of amifampridine phosphate were established for at least 7 days, and at least a 2-point improvement in MG-ADL score was achieved. 70 patients were recruited, 19 were screen failures.

Pre-assignment period milestones

Number of subjects started	89
Number of subjects completed	70

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 19

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a double-blind, treatment withdrawal study where both the patient and Investigator were blinded to the treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Amifampridine phosphate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	3,4-pyridinediamine, phosphate (1:1) diamino-3,4-pyridine, phosphate salt
Investigational medicinal product code	
Other name	3,4-diaminopyridine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The selection and timing of doses for each subject were determined at the discretion of the investigator within the bounds of a total daily dose of 30 mg to 80 mg, divided into doses taken 3 to 4 times per day, based on optimal neuromuscular benefit. The maximum single dose was 20 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:

Each tablet contains microcrystalline cellulose, colloidal anhydrous silica, and calcium stearate. Placebo was provided as tablets indistinguishable from amifampridine phosphate.

Number of subjects in period 1[1]	Amifampridine phosphate	Placebo
Started	34	36
Completed	34	35
Not completed	0	1
Adverse event, non-fatal	-	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: The worldwide number enrolled in the trial includes also patients who failed the pre-screening phase.

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	34	36	70
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	53.1	53.5	
standard deviation	± 14.92	± 12.61	-
Gender categorical			
Units: Subjects			
Female	24	8	32
Male	10	28	38
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	3	2	5
Native Hawaiian or Other Pacific Islander	0	0	0
White	31	34	65
Other	0	0	0
Not recorded	0	0	0
Weight			
Units: Kg			
arithmetic mean	84.6	84.3	
standard deviation	± 21.11	± 27.27	-
Height			
Units: cm			
arithmetic mean	164.7	163.5	
standard deviation	± 7.64	± 10.75	-

MG-ADL total score			
MG-ADL total score at baseline for MuSK subjects (n=27 in the Amifampridine group and n=28 in the placebo group)			
Units: Score			
arithmetic mean	4.96	3.86	
standard deviation	± 2.915	± 2.103	-
MG-ADL Total Score for AChR subjects			
MG-ADL Total Score for AChR (n=7 in the Amifampridine group and n=8 in the placebo group)			
Units: Score			
arithmetic mean	6.14	7.00	
standard deviation	± 3.388	± 4.175	-
QMG Total Score for MuSK subjects			
At baseline n=27 in the Amfridine group and n=28 in the placebo group.			
Units: Score			
arithmetic mean	10.00	8.64	
standard deviation	± 3.873	± 3.744	-

End points

End points reporting groups

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

Primary: Change in MG-ADL score from Day 0 to Day 10_MuSK-MG

End point title	Change in MG-ADL score from Day 0 to Day 10_MuSK-MG

End point description:

The primary efficacy variable was the change in MG-ADL score from Day 0 (Baseline) to Day 10 for MuSK-MG subjects treated with amifampridine phosphate and placebo.
The MG-ADL is a self-report scale designed to assess the patient's MG symptoms and functional performance of activities of daily living. The MG-ADL consists of 8 items (derived from symptom-based components of the original 13-item Quantitative Myasthenia Gravis test) to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. Each of the 8 items is rated using a response scale ranging from 0 (normal) to 3 (most severe). Lower scores indicate better functional performance.
Data of patients diagnosed with MuSK-MG were reported.

End point type	Primary

End point timeframe:

From Day 0 (baseline) to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Score				
arithmetic mean (standard deviation)	1.04 (± 2.980)	2.25 (± 2.00)		

Statistical analyses

Statistical analysis title	Change in MG-ADL score from Day 0 to Day 10

Statistical analysis description:

Observed significance level (p-value) for Wilcoxon-Mann-Whitney Test of Equality of CFB distributions

Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2196 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - These results were not statistically significant (p = 0.2196) and provided no support for the alternative hypothesis.

Secondary: Change in QMG score from Day 0 to Day 10_MuSK-MG	
End point title	Change in QMG score from Day 0 to Day 10_MuSK-MG

End point description:

The QMG score was used to assess the patient’s general body strength and fatigability. The QMG was administered at the protocol-specified time points by the same evaluator throughout the study.

End point type	Secondary

End point timeframe:

From Day 0 to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Score				
arithmetic mean (standard deviation)	1.19 (± 3.990)	1.80 (± 3.948)		

Statistical analyses

Statistical analysis title	Change in QMG score from Day 0 to Day 10
Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.3736
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Observed significance level (p-value) for Wilcoxon-Mann-Whitney Test of Equality of CFB distributions

Secondary: Change in QMG score from Day 0 to Day 10_AChR	
End point title	Change in QMG score from Day 0 to Day 10_AChR

End point description:

The QMG score was used to assess the patient’s general body strength and fatigability. The QMG was administered at the protocol-specified time points by the same evaluator throughout the study.

End point type	Secondary

End point timeframe:

From Day 0 to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Score				
arithmetic mean (standard deviation)	10.57 (± 3.359)	14.13 (± 4.155)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with a change of 2 or more in MG-ADL score from Baseline to Day 10

End point title	Proportion of subjects with a change of 2 or more in MG-ADL score from Baseline to Day 10

End point description:

End point type	Secondary

End point timeframe:

From Day 0 to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: subject				
Less Than 2 Points	21	25		
2 or More Points	6	3		

Statistical analyses

Statistical analysis title	MG-ADL Score Shift of at Least 2 Points

Statistical analysis description:

Six (6) subjects (22.2%) randomized to treatment with amifampridine phosphate were observed to have a change in MG-ADL score of 2 or more while three (3) subjects (10.7%) randomized to treatment with placebo were observed to have a change in MG-ADL score of 2 or more.

Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.2955
Method	Fisher exact

Notes:

[3] - While more subjects in the amifampridine treatment group had a change in MG-ADL score of 2 or more compared to the placebo treatment group, these differences were not statistically significant.

Secondary: Proportion of a subjects with a change of 3 or more in QMG score from Baseline to Day 10 for MuSK-MG subjects

End point title	Proportion of a subjects with a change of 3 or more in QMG

	score from Baseline to Day 10 for MuSK-MG subjects

End point description:

Three (3) subjects (11.5%) randomized to treatment with amifampridine phosphate were observed to have a change in QMG score of 3 or more while one (1) subject (4.0%) randomized to treatment with placebo was observed to have a change in QMG score of 3 or more.

End point type	Secondary

End point timeframe:

From Day 0 to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: subject				
Less Than 3 Points	23	24		
3 or More Points	3	1		

Statistical analyses

Statistical analysis title	QMG Score Shift
Comparison groups	Amifampridine phosphate v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.6098
Method	Fisher exact

Notes:

[4] - While more subjects in the amifampridine treatment group had a change in QMG score of 3 or more compared to the placebo treatment group, these differences were not statistically significant.

Other pre-specified: Change in MG-ADL score from Day 0 to Day 10_AChR

End point title	Change in MG-ADL score from Day 0 to Day 10_AChR

End point description:

The MG-ADL is a self-report scale designed to assess the patient's MG symptoms and functional performance of activities of daily living. The MG-ADL consists of 8 items (derived from symptom-based components of the original 13-item Quantitative Myasthenia Gravis test) to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. Each of the 8 items is rated using a response scale ranging from 0 (normal) to 3 (most severe). Lower scores indicate better functional performance.
Data of AChR subjects were reported.

End point type	Other pre-specified

End point timeframe:

From Day 0 to Day 10

End point values	Amifampridine phosphate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Score				
arithmetic mean (standard deviation)	-1.43 (± 2.225)	3.38 (± 2.825)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the enrollment to the end of the study.

Adverse event reporting additional description:

Safety was assessed through the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs). Vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests, physical examinations, and concomitant medications were also evaluated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

The Safety population consisted of all subjects who were enrolled in the study and had received at least one dose of amifampridine phosphate. (Subjects who began the run-in period belonged to the Safety population whether they were randomized to a treatment or not).

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 86 (2.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Myasthenia gravis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis crisis			
subjects affected / exposed	1 / 86 (1.16%)		
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	80 / 86 (93.02%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumor benign			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	9		
Dropped head syndrome			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Facial paresis			
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	11		
Hypoaesthesia			
subjects affected / exposed	4 / 86 (4.65%)		
occurrences (all)	4		

Hypogeusia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Myasthenia gravis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Myasthenia gravis crisis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	35 / 86 (40.70%)		
occurrences (all)	35		
Sensory disturbance			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Sinus headache			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Speech disorder			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	10		
Feeling cold			

subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Feeling hot			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Feeling jittery			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Medical device site discharge			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Temperature regulation disorder			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	5		
Abdominal distention			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	8		

Diarrhoea			
subjects affected / exposed	12 / 86 (13.95%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	7		
Dysphagia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Eructation			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Hypoaesthesia oral			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	14 / 86 (16.28%)		
occurrences (all)	14		
Paraesthesia oral			
subjects affected / exposed	37 / 86 (43.02%)		
occurrences (all)	37		
Tongue coated			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Dyspnoea			

subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Sinus congestion			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Disorientation			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	6		
Muscular weakness			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	4 / 86 (4.65%)		
occurrences (all)	4		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Ear infection			

subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	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

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

The COVID-19 Pandemic occurred at the end of the study. Four enrolled subjects were impacted by the COVID-19 Pandemic. There were no statistically significant impacts on the results of the study due to the COVID-19 Pandemic.

Notes: