Clinical trial results:
A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension

Summary

EudraCT number	2017-002447-15
Trial protocol	GB DK DE HU IT
Global end of trial date	10 February 2020

Results information

Result version number	v1 (current)
This version publication date	01 May 2021
First version publication date	01 May 2021
Summary attachment (see zip file)	SPIMM-301 CSR Sumamry (SPIMM-301 CSR Synopsis.docx)

Trial information

Trial identification

Sponsor protocol code	SPIMM-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03323749
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Stealth BioTheraeputics Inc.
Sponsor organisation address	140 Kendrick Street Building C-West, Needham, United States, MA 02494
Public contact	Chief Clinical Development Officer, Stealth BioTherapeutics Inc., +1 6177622503, Jim.Carr@stealthbt.com
Scientific contact	Chief Clinical Development Officer, Stealth BioTherapeutics Inc., +1 6177622503, Jim.Carr@stealthbt.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 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2020
Global end of trial reached?	Yes
Global end of trial date	10 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of PART 1 is to evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks on the:
• Distance Walked on the 6MWT
• Total Fatigue on the Primary Mitochondrial Myopathy Symptom Assessment© (PMMSA)

The PART 2 objective is to assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 144 weeks.

Protection of trial subjects:

This pivotal trial was conducted in strict accordance with the current versions of the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and all applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2017
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	United States: 118
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 41
Worldwide total number of subjects	218
EEA total number of subjects	72

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)	7
Adults (18-64 years)	193
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multicenter trial: 27 sites in Canada, Denmark, Germany, Hungary, Italy, the United Kingdom, and the United States.
09 Oct 2017 (First subject's informed consent date) Part 1: 03 Nov 2017 (First subject's dose date) to 04 Nov 2019 (Last subject's last visit or contact)
Part 2: 30 Apr 2018 (First subject's dose date) to 10 Feb 2020

Pre-assignment

Screening details:

Subjects were ≥16 and ≤80 years of age (≥18 years of age in Germany), diagnosed with PMM (adjudicated molecular genetic abnormality of the mitochondrial respiratory chain and subject reported symptoms). Subjects who walked <100 m or >450 m during the 6MWT at the Screening Visit or the Baseline Visit were not eligible for the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Elamipretide Then Open-Label Elamipretide

Arm description:

Patients in this arm have been initially randomised to elamipretide (in the double-blind period) followed by elamipretide in the open-label period.

Arm type	Experimental
Investigational medicinal product name	elamipretide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg (0.5 mL) elamipretide subcutaneous (SC) daily

Arm title	Double-Blind Placebo, Then Open-Label Elamipretide

Arm description:

Patients in this arm have been initially randomised to placebo (in the double-blind period) followed by elamipretide in the open-label period.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL placebo subcutaneous (SC) daily

Number of subjects in period 1	Double-Blind Elamipretide Then Open-Label Elamipretide	Double-Blind Placebo, Then Open-Label Elamipretide
Started	109	109
Completed	102	103
Not completed	7	6
Adverse event, non-fatal	3	1
Lost to follow-up	4	5

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Elamipretide, Then Open Label Elamipretide

Arm description:

Patients in this arm have been initially randomised to elamipretide (in the double-blind period) followed by elamipretide in the open-label period.

Arm type	Experimental
Investigational medicinal product name	elamipretide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg (0.5 mL) elamipretide subcutaneous (SC) daily

Arm title	Double-Blind Placebo Then Open-Label Elamipretide

Arm description:

Patients in this arm have been initially randomised to placebo (in the double-blind period) followed by elamipretide in the open-label period.

Arm type	Experimental
Investigational medicinal product name	elamipretide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg (0.5 mL) elamipretide subcutaneous (SC) daily

Number of subjects in period 2[1]	Double-Blind Elamipretide, Then Open Label Elamipretide	Double-Blind Placebo Then Open-Label Elamipretide
Started	93	103
Completed	0	0
Not completed	93	103
Termination due Sponsor decision	93	103

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 9 subjects did not wish to continue from Part 1 to Part 2

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Elamipretide Then Open-Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to elamipretide (in the double-blind period) followed by elamipretide in the open-label period.	
Reporting group title	Double-Blind Placebo, Then Open-Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to placebo (in the double-blind period) followed by elamipretide in the open-label period.	

Reporting group values	Double-Blind Elamipretide Then Open-Label Elamipretide	Double-Blind Placebo, Then Open-Label Elamipretide	Total
Number of subjects	109	109	218
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	45.5	44.3	
standard deviation	± 15.7	± 14.3	-
Gender categorical Units: Subjects			
Female	67	73	140
Male	42	36	78

End points

End points reporting groups

Reporting group title	Double-Blind Elamipretide Then Open-Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to elamipretide (in the double-blind period) followed by elamipretide in the open-label period.	
Reporting group title	Double-Blind Placebo, Then Open-Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to placebo (in the double-blind period) followed by elamipretide in the open-label period.	
Reporting group title	Double-Blind Elamipretide, Then Open Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to elamipretide (in the double-blind period) followed by elamipretide in the open-label period.	
Reporting group title	Double-Blind Placebo Then Open-Label Elamipretide
Reporting group description:	
Patients in this arm have been initially randomised to placebo (in the double-blind period) followed by elamipretide in the open-label period.	

Primary: Six-minute Walk Test (6MWT)

End point title	Six-minute Walk Test (6MWT)
End point description:	
Change From Baseline in Distance Walked (meters) on the Six-Minute Walk Test by Visit	
End point type	Primary
End point timeframe:	
Baseline to 24 weeks	

End point values	Double-Blind Elamipretide Then Open-Label Elamipretide	Double-Blind Placebo, Then Open-Label Elamipretide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: meters				
arithmetic mean (standard deviation)	15.33 (± 61.48)	17.38 (± 51.69)		

Statistical analyses

Statistical analysis title	Efficacy analyses

Statistical analysis description:

The distance walked (meters) during the 6MWT and Total Fatigue score on the PMMSA constituted the primary endpoint family. A family-wise alpha level of 0.05 was maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 24 weeks. If both primary endpoints were significantly different from placebo at the 0.05 (two-sided) level of significance (in favor of

treatment), then both were considered statistically significant.

Comparison groups	Double-Blind Elamipretide Then Open-Label Elamipretide v Double-Blind Placebo, Then Open-Label Elamipretide
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.025
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[1] - two-sided

Primary: Total Fatigue Score on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

End point title	Total Fatigue Score on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

End point description:

Change from Baseline in Total fatigue score on the on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) by visit. Each individual item score ranges from 1 (none) to 4 (severe). The total fatigue score ranges from 4-16. Lower values represent a better outcome. The total fatigue score is the sum of question 1 through question 4 on the Primary Mitochondrial Myopathy Symptom Assessment.

End point type	Primary

End point timeframe:

Baseline to 24 weeks

End point values	Double-Blind Elamipretide Then Open-Label Elamipretide	Double-Blind Placebo, Then Open-Label Elamipretide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	101		
Units: Score				
arithmetic mean (standard deviation)	-1.18 (± 2.13)	-1.09 (± 2.44)		

Statistical analyses

Statistical analysis title	Efficacy analyses

Statistical analysis description:

The distance walked (meters) during the 6MWT and Total Fatigue score on the PMMSA constituted the primary endpoint family. A family-wise alpha level of 0.05 was maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 24 weeks. If both primary endpoints were significantly different from placebo at the 0.05 (two-sided) level of significance (in favor of treatment), then both were considered statistically significant.

Comparison groups	Double-Blind Elamipretide Then Open-Label Elamipretide v Double-Blind Placebo, Then Open-Label Elamipretide

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.025
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[2] - two-sided significance

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Period 1 and Period 2	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Double-Blind Elamipretide
Reporting group description: Double-blind period: elamipretide: 40 mg of elamipretide administered as once daily 0.5 mL subcutaneous injections for 24 weeks using the elamipretide delivery system.	
Reporting group title	Double-Blind Placebo
Reporting group description: Double-blind period: placebo comparator: Placebo administered as once daily 0.5 mL subcutaneous injections for 24 weeks using the elamipretide delivery system.	
Reporting group title	Open-Label Elamipretide
Reporting group description: Double blind period: elamipretide: 40mg (0.5mL) of elamipretide administered as once daily 0.5 mL subcutaneous injections for 24 weeks using the elamipretide delivery system, then elamipretide open-label treatment: 40 mg of elamipretide administered as once daily 0.5 mL subcutaneous injections for up to 144 weeks using the elamipretide delivery system.	
Reporting group title	Open-Label Placebo
Reporting group description: Double-blind period: placebo comparator: Placebo administered as once daily 0.5 mL subcutaneous injections for 24 weeks using the elamipretide delivery system. Open-label period: 40 mg of elamipretide administered as once daily 0.5 mL subcutaneous injections for up to 144 weeks using the elamipretide delivery system.	

Serious adverse events	Double-Blind Elamipretide	Double-Blind Placebo	Open-Label Elamipretide
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 109 (4.59%)	3 / 109 (2.75%)	12 / 93 (12.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			

subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labile blood pressure			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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			
Asthma			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal laceration			

subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
MELAS syndrome			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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
Coronary artery dissection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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
Hemiplegia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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
Hypoaesthesia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychogenic seizure			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			

subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	0 / 93 (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			
Urinary retention			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 109 (0.92%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral sinusitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 103 (8.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Labile blood pressure			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vaginal laceration			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
MELAS syndrome			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery dissection			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemiplegia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychogenic seizure			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Duodenal ulcer haemorrhage				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 103 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal pseudo-obstruction				
subjects affected / exposed	0 / 103 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 103 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Urticaria				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary retention				
subjects affected / exposed	0 / 103 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc disorder				
subjects affected / exposed	0 / 103 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis				

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral sinusitis			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Double-Blind Elamipretide	Double-Blind Placebo	Open-Label Elamipretide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 109 (98.17%)	83 / 109 (76.15%)	88 / 93 (94.62%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	4 / 93 (4.30%)
occurrences (all)	0	0	4
Blood glucose increased			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Blood lactic acid increased			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Eosinophil count increased			
subjects affected / exposed	7 / 109 (6.42%)	0 / 109 (0.00%)	7 / 93 (7.53%)
occurrences (all)	7	0	7
Weight decreased			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 109 (5.50%)	3 / 109 (2.75%)	8 / 93 (8.60%)
occurrences (all)	6	3	8
Skin abrasion			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 109 (5.50%)	3 / 109 (2.75%)	1 / 93 (1.08%)
occurrences (all)	6	3	1
Headache			

subjects affected / exposed	8 / 109 (7.34%)	4 / 109 (3.67%)	5 / 93 (5.38%)
occurrences (all)	8	4	5
Hypoaesthesia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	3 / 93 (3.23%)
occurrences (all)	0	0	3
Fatigue			
subjects affected / exposed	4 / 109 (3.67%)	4 / 109 (3.67%)	4 / 93 (4.30%)
occurrences (all)	4	4	4
Injection site erythema			
subjects affected / exposed	94 / 109 (86.24%)	31 / 109 (28.44%)	66 / 93 (70.97%)
occurrences (all)	94	31	66
Injection site induration			
subjects affected / exposed	31 / 109 (28.44%)	6 / 109 (5.50%)	25 / 93 (26.88%)
occurrences (all)	31	6	25
Injection site injury			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	43 / 109 (39.45%)	20 / 109 (18.35%)	32 / 93 (34.41%)
occurrences (all)	43	20	32
Injection site pruritus			
subjects affected / exposed	82 / 109 (75.23%)	10 / 109 (9.17%)	57 / 93 (61.29%)
occurrences (all)	82	10	57
Injection site swelling			

subjects affected / exposed	42 / 109 (38.53%)	7 / 109 (6.42%)	29 / 93 (31.18%)
occurrences (all)	42	7	29
Pyrexia			
subjects affected / exposed	2 / 109 (1.83%)	3 / 109 (2.75%)	0 / 93 (0.00%)
occurrences (all)	2	3	0
Injection site bruising			
subjects affected / exposed	9 / 109 (8.26%)	18 / 109 (16.51%)	5 / 93 (5.38%)
occurrences (all)	9	18	5
Injection site haematoma			
subjects affected / exposed	0 / 109 (0.00%)	7 / 109 (6.42%)	0 / 93 (0.00%)
occurrences (all)	0	7	0
Injection site haemorrhage			
subjects affected / exposed	7 / 109 (6.42%)	10 / 109 (9.17%)	2 / 93 (2.15%)
occurrences (all)	7	10	2
Injection site mass			
subjects affected / exposed	9 / 109 (8.26%)	2 / 109 (1.83%)	4 / 93 (4.30%)
occurrences (all)	9	2	4
Injection site nodule			
subjects affected / exposed	11 / 109 (10.09%)	2 / 109 (1.83%)	8 / 93 (8.60%)
occurrences (all)	11	2	8
Injection site urticaria			
subjects affected / exposed	14 / 109 (12.84%)	0 / 109 (0.00%)	12 / 93 (12.90%)
occurrences (all)	14	0	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	3 / 93 (3.23%)
occurrences (all)	0	0	3
Constipation			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	3 / 93 (3.23%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	5 / 109 (4.59%)	8 / 109 (7.34%)	4 / 93 (4.30%)
occurrences (all)	5	8	4
Diarrhoea			
subjects affected / exposed	3 / 109 (2.75%)	9 / 109 (8.26%)	3 / 93 (3.23%)
occurrences (all)	3	9	3

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 109 (3.67%)	1 / 109 (0.92%)	3 / 93 (3.23%)
occurrences (all)	4	1	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	3 / 93 (3.23%)
occurrences (all)	0	0	3
Back pain			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	4 / 93 (4.30%)
occurrences (all)	0	0	4
Muscle spasms			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	4 / 93 (4.30%)
occurrences (all)	0	0	4
Muscular weakness			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	3 / 93 (3.23%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	1 / 109 (0.92%)	5 / 109 (4.59%)	2 / 93 (2.15%)
occurrences (all)	1	5	2
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	8 / 109 (7.34%)	2 / 109 (1.83%)	6 / 93 (6.45%)
occurrences (all)	8	2	6
Pneumonia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 109 (0.00%)	2 / 93 (2.15%)
occurrences (all)	1	0	2
Sinusitis			

subjects affected / exposed	2 / 109 (1.83%)	3 / 109 (2.75%)	2 / 93 (2.15%)
occurrences (all)	2	3	2
Upper respiratory tract infection			
subjects affected / exposed	7 / 109 (6.42%)	7 / 109 (6.42%)	7 / 93 (7.53%)
occurrences (all)	7	7	7
Urinary tract infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 109 (0.00%)	4 / 93 (4.30%)
occurrences (all)	0	0	4

Non-serious adverse events	Open-Label Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 103 (99.03%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Blood lactic acid increased			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Eosinophil count increased			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	7		
Skin abrasion			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Hypoaesthesia			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		
Injection site erythema			
subjects affected / exposed	87 / 103 (84.47%)		
occurrences (all)	87		
Injection site induration			
subjects affected / exposed	41 / 103 (39.81%)		
occurrences (all)	41		
Injection site injury			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		

Injection site pain			
subjects affected / exposed	37 / 103 (35.92%)		
occurrences (all)	37		
Injection site pruritus			
subjects affected / exposed	81 / 103 (78.64%)		
occurrences (all)	81		
Injection site swelling			
subjects affected / exposed	20 / 103 (19.42%)		
occurrences (all)	20		
Pyrexia			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences (all)	0		
Injection site bruising			
subjects affected / exposed	15 / 103 (14.56%)		
occurrences (all)	15		
Injection site haematoma			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences (all)	0		
Injection site haemorrhage			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences (all)	8		
Injection site mass			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		
Injection site nodule			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences (all)	8		
Injection site urticaria			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences (all)	8		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	2 / 103 (1.94%) 2 2 / 103 (1.94%) 2 6 / 103 (5.83%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 3 / 103 (2.91%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 2 / 103 (1.94%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 2 / 103 (1.94%) 2 2 / 103 (1.94%) 2 0 / 103 (0.00%) 0 1 / 103 (0.97%) 1 5 / 103 (4.85%) 5		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	 2 / 103 (1.94%) 2		

Nasopharyngitis			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	0 / 103 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2017	Main changes include but are not limited to: Added language to provide additional clarity to sites with regard to the 6MWT, QTc prolongation and the virus (HIV), hepatitis B, or hepatitis C infection. Added additional analytes that will be analyzed.
22 December 2017	Main changes include but are not limited to: Updated language to align with summary nonclinical study safety findings from the Investigator's Brochure v10.0 (Sections 1.2. and 1.5.), which was updated on 22 December 2017; Removed the maximum number of subjects since the risk:benefit does not change at exactly 222 participants. The study will still enroll approximately 202 subjects; Updated text to provide clarity that the decision for a subject to continue into PART 2 requires the Investigator's review of the PART 2 Continuation Criteria; Updated text to provide guidance that the C-SSRS Baseline/Screening should be completed at the Screening Visit; Added text to provide guidance of what constitutes enrollment in SPIMM-300; Updated text to provide guidance that the repeat ECGs must occur during the same visit; Added section to provide background information on the elamipretide pen injector and its classification status in multiple countries/regions; Added language to provide guidance if an Investigator wishes to rechallange a subject on the IMP.
15 June 2018	Main changes include but are not limited to: To provide clarity about planned analyses; To provide an option for subjects who did not participate in SPIMM-300 to enroll in SPIMM-301 and to note their screening period may be longer than 28 days; To clarify subjects who do not continue in PART 2 will not be administered IMP at the Week 24 visit and those who do continue will be administered PART 2 drug supply; To clarify the order of assessments performed; To note the collection of genetic testing results from subjects not previously enrolled in SPIMM-300 and assessment of pre-treatment events; To clarify study conduct and IMP administration; To provide the blood sample for assessing the immunogenicity potential of the IMP; To note the review of genetic testing results from subjects not previously enrolled in SPIMM-300 and to note genetic testing will not be provided as part of the SPIMM-301 trial; To clarify the additional ISR assessments performed during the extended study duration; To define the study subject population and to provide clarification; To clarify eligibility criteria for PART 2; To provide examples of situations that an Investigator may consider subject discontinuation; To update text about the elamipretide pen injector; To provide instruction regarding IMP administration for subjects receiving concomitant therapy SC injections; To clarify how IMP is to be dispensed and stored; To clarify the definition of ADE and SADE; To clarify eGFR is being calculated from the safety laboratory tests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

10 February 2020	At the completion of Part 1, the database for Part 1 was locked and the final analyses for Part 1 conducted, while Part 2 remained ongoing. Following review of the final analyses for Part 1, Stealth BioTherapeutics decided to terminate the open trials evaluating elamipretide in subjects with PMM. Due to this, Part 2 of the trial was terminated early. Therefore, trial visits and phone calls occurred until trial termination, and the Part 2 Follow-up Period for each active subject began after they were discontinued early due to trial termination.	-

Notes:

Limitations and caveats

None reported