Clinical trial results:
A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of 4 Weeks Treatment with Subcutaneous Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Preserved Ejection Fraction.

Summary

EudraCT number	2015-005615-32
Trial protocol	DE
Global end of trial date	28 September 2020
Results information	
Result version number	v1 (current)
This version publication date	19 December 2020
First version publication date	19 December 2020
Summary attachment (see zip file)	SPIHF-203 Synopsis (Synopsis.docx)

Trial information

Trial identification	
Sponsor protocol code	SPIHF-203
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Stealth BioTherapeutics, Inc.
Sponsor organisation address	275 Grove Street, Suite 3-107, Newton, United States, MA 02466
Public contact	Matthew Millstein, Stealth BioTherapeutics Inc., 001 6177622539, matthew.millstein@stealthbt.com
Scientific contact	Matthew Millstein, Stealth BioTherapeutics Inc., 001 6177622539, matthew.millstein@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	04 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2017
Global end of trial reached?	Yes
Global end of trial date	28 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study is to evaluate the effects of 4 weeks of daily SC administration of elamipretide on the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') at rest as assessed by transthoracic echocardiography.

Protection of trial subjects:

This study was conducted in strict accordance with the Council for International Organizations of Medical Sciences International Ethical Guidelines, ICH GCP guideline, and all applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 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	Germany: 10
Country: Number of subjects enrolled	Serbia: 37
Worldwide total number of subjects	47
EEA total number of subjects	10

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)	9
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited in 2 countries in Europe (Germany and Serbia) at 9 study centers.

Pre-assignment

Screening details:

Subjects' study eligibility was determined during the Screening period, which began with the signature of the ICF and lasted up to 7 days. Tests and assessments were performed. Subjects who met all study requirements, including all inclusion and none of the exclusion criteria, entered the Treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Elamipretide 40 mg

Arm description:

A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care. Study medication was administered in the abdomen (rotating clockwise around the 4 abdominal quadrants) by either the clinical site staff or a visiting nurse.

Arm type	Experimental
Investigational medicinal product name	Elamipretide
Investigational medicinal product code	
Other name	MTP-131
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg administered subcutaneously once daily for 28 consecutive days

Arm title	Placebo

Arm description:

A 4 weeks treatment with placebo handled and administered identically to the active drug.

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:

Subjects randomized to placebo received a subcutaneous injection containing 1 mL of sterile solution once daily

Number of subjects in period 1	Elamipretide 40 mg	Placebo
Started	23	24
Completed	22	23
Not completed	1	1
Consent withdrawn by subject	-	1
Subject's request	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Elamipretide 40 mg

Arm description:

A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care. Study medication was administered in the abdomen (rotating clockwise around the 4 abdominal quadrants) by either the clinical site staff or a visiting nurse.

Arm type	Experimental
Investigational medicinal product name	Elamipretide
Investigational medicinal product code	
Other name	MTP-131
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg administered subcutaneously once daily for 28 consecutive days

Arm title	Placebo

Arm description:

A 4 weeks treatment with placebo handled and administered identically to the active drug.

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:

Subjects randomized to placebo received a subcutaneous injection containing 1 mL of sterile solution once daily

Number of subjects in period 2	Elamipretide 40 mg	Placebo
Started	22	23
Completed	22	23

Baseline characteristics

Reporting groups

Reporting group title	Elamipretide 40 mg

Reporting group description:

A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care. Study medication was administered in the abdomen (rotating clockwise around the 4 abdominal quadrants) by either the clinical site staff or a visiting nurse.

Reporting group title	Placebo

Reporting group description:

A 4 weeks treatment with placebo handled and administered identically to the active drug.

Reporting group values	Elamipretide 40 mg	Placebo	Total
Number of subjects	23	24	47
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	4	9
From 65-84 years	18	20	38
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	16	14	30
Male	7	10	17

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Endpoint were analyzed using modified intention-to-treat (mITT) population, which included all study subjects who received at least 1 dose of IMP.

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

Subject analysis set description:

Safety Population (i.e. all study subjects who received at least 1 dose of IMP) was used for Safety analysis.

Reporting group values	mITT	Safety Population	
Number of subjects	47	47	
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	9	9	
From 65-84 years	38	38	
85 years and over			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Elamipretide 40 mg
Reporting group description:	
A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care. Study medication was administered in the abdomen (rotating clockwise around the 4 abdominal quadrants) by either the clinical site staff or a visiting nurse.	
Reporting group title	Placebo
Reporting group description:	
A 4 weeks treatment with placebo handled and administered identically to the active drug.	
Reporting group title	Elamipretide 40 mg
Reporting group description:	
A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care. Study medication was administered in the abdomen (rotating clockwise around the 4 abdominal quadrants) by either the clinical site staff or a visiting nurse.	
Reporting group title	Placebo
Reporting group description:	
A 4 weeks treatment with placebo handled and administered identically to the active drug.	
Subject analysis set title	mITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Endpoint were analyzed using modified intention-to-treat (mITT) population, which included all study subjects who received at least 1 dose of IMP.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Population (i.e. all study subjects who received at least 1 dose of IMP) was used for Safety analysis.	

Primary: Changes in septal E/e’ at rest between Visit 1 and Visit 5

End point title	Changes in septal E/e’ at rest between Visit 1 and Visit 5
End point description:	
End point type	Primary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.7 (± 3.08)	0.1 (± 4.52)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Placebo v Elamipretide 40 mg
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Primary: Change in lateral E/e' at Rest from Visit 1 to Visit 5	
End point title	Change in lateral E/e' at Rest from Visit 1 to Visit 5
End point description:	

End point type	Primary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.5 (± 3.80)	-1.1 (± 3.82)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Primary: Change in average E/e' at Rest from Visit 1 to Visit 5	
End point title	Change in average E/e' at Rest from Visit 1 to Visit 5
End point description:	

End point type	Primary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.5 (± 3.22)	-0.6 (± 3.50)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Secondary: Changes in septal E/e' at maximum workload from Visit 1 to Visit 5

End point title	Changes in septal E/e' at maximum workload from Visit 1 to Visit 5

End point description:

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-1.0 (± 5.11)	6.66 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LV systolic GLS at rest from Visit 1 to Visit 5

End point title	Change in LV systolic GLS at rest from Visit 1 to Visit 5

End point description:

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	0.8 (± 2.71)	-0.7 (± 2.64)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	ANCOVA

Secondary: Change in LV systolic GLS during maximal workload from Visit 1 to Visit 5

End point title	Change in LV systolic GLS during maximal workload from Visit 1 to Visit 5

End point description:

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-3.1 (± 5.61)	-0.3 (± 3.20)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Secondary: Change in 6MWT from Visit 1 to Visit 5

End point title	Change in 6MWT from Visit 1 to Visit 5
End point description:	
End point type	Secondary
End point timeframe: Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	29.6 (± 55.33)	28.1 (± 69.79)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Secondary: Change in NT proBNP (log-transformed) from Visit 1 to Visit 5	
End point title	Change in NT proBNP (log-transformed) from Visit 1 to Visit 5
End point description:	

End point type	Secondary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.1 (± 0.52)	-0.0 (± 0.53)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Secondary: Change in lateral E/e' At Maximal Workload from Visit 1 to Visit 5	
End point title	Change in lateral E/e' At Maximal Workload from Visit 1 to Visit 5
End point description:	

End point type	Secondary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-1.3 (± 4.15)	-2.0 (± 4.81)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Secondary: Change in average E/e' At Maximal Workload from Visit 1 to Visit 5

End point title	Change in average E/e' At Maximal Workload from Visit 1 to Visit 5
End point description:	
End point type	Secondary
End point timeframe: Visit 1 to Visit 5	

End point values	Elamipretide 40 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: unit(s)				
arithmetic mean (standard deviation)	-1.4 (± 4.02)	-1.4 (± 4.20)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) model
Comparison groups	Elamipretide 40 mg v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The period between the first dose of study treatment and 30 days after the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Elamipretide 40 mg
Reporting group description:	
A 4 week treatment with 40 mg elamipretide administered subcutaneously once daily on top of usual care	
Reporting group title	Placebo
Reporting group description:	
A 4 weeks treatment with placebo handled and administered identically to the active drug.	

Serious adverse events	Elamipretide 40 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Elamipretide 40 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 23 (60.87%)	6 / 24 (25.00%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Subcutaneous haematoma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	9	1	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	5 / 23 (21.74%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Application site erythema			
subjects affected / exposed	4 / 23 (17.39%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Injection site swelling			
subjects affected / exposed	4 / 23 (17.39%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Injection site pruritus			

subjects affected / exposed	2 / 23 (8.70%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Application site bruise			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Application site oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Application site pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Application site pruritus			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Injection site reaction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Asymptomatic bacteriuria			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2016	Amendment 1 (Version 4.0) implemented changes to study procedures and inclusion/exclusion criteria due to requirements of the Ethics Committee, clarified efficacy measures, and added information regarding SAE reporting and other regulatory considerations.
23 May 2016	Amendment 2 (Version 5.0), implemented further changes to inclusion/exclusion criteria, clarified the schedule of INR determinations for subjects in Serbia vs those in Germany, and required for Serbian sites that study drug be administered at the clinical site/hospital. In addition, general formatting and other administrative changes were made throughout the document.
01 November 2016	Amendment 3 (Version 6.0), implemented several updates to the study protocol in an effort to improve subject recruitment and reduce the high number of screening failures. Examples of these changes included increasing the maximum number of study sites from 8 to 9, changes to inclusion and exclusion criteria, updates to primary and secondary efficacy measures, and allowance for laboratory screening values to be measured locally for purposes of randomization

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported