

**Clinical trial results:****A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction****Summary**

EudraCT number	2014-005724-10
Trial protocol	NL GB IT
Global end of trial date	12 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019
Summary attachment (see zip file)	Synopsis (Synopsis SPIHF-201.docx)

Trial information**Trial identification**

Sponsor protocol code	SPIHF-201
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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, Newton, United States, MA 02466
Public contact	Julia Morteo, Stealth BioTherapeutics Inc., 1 0016174314216, julia.morteo@stealthbt.com
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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	16 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2017
Global end of trial reached?	Yes
Global end of trial date	12 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of multiple subcutaneous (SC) doses of elamipretide on left ventricular end systolic volume (LV ESV) assessed by cardiac Magnetic Resonance Imaging (MRI)

Protection of trial subjects:

The Declaration of Helsinki, Patient Informed Consent, International Council for Harmonisation guideline on Good Clinical Practice (ICH-GCP).

Background therapy:

Heart failure (HF) treatment, including, but not limited to, angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), and an evidence-based beta blocker for the treatment of HF. Subjects who could not tolerate ACEI or ARB due to reduced renal function or hypotension were eligible. Subjects could be receiving aldosterone antagonists, but this was not a requirement for the study.

Evidence for comparator: -

Actual start date of recruitment	20 June 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	Netherlands: 27
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 41
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	34
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 15 sites in 3 countries (Italy, The Netherlands, and United Kingdom), with 14 sites consenting at least 1 subject.

Pre-assignment

Screening details:

Subjects ≥ 40 and < 80 years with known history of chronic ischemic or non-ischemic cardiomyopathy of at least 6 months duration or signs and symptoms consistent with stable heart failure (HF) receiving HF treatment (stable doses ≥ 1 month, with normal sinus rhythm, and left ventricular ejection fraction (LVEF) $\leq 40\%$ by 2-D echocardiography.

Period 1

Period 1 title	Screening
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description:

Not applicable

Arm type	Placebo
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Solution for injection
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Routes of administration	Subcutaneous use
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Dosage and administration details:

Not applicable

Arm title	4 mg elamipretide
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Arm description:

Not applicable

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

Not applicable

Arm title	40 mg elamipretide
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Arm description:

Not applicable

Arm type	Experimental
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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:

Not applicable

Number of subjects in period 1	Placebo	4 mg elamipretide	40 mg elamipretide
Started	24	22	25
Completed	24	22	25

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

At Day 1, after the eligibility criteria was confirmed, a treatment kit number was assigned to each subject based on a centralized computer generated randomization schedule administered by Interactive web-based response system (IWRS). Subjects were randomized into 1 of 3 treatment groups in a 1:1:1 fashion to receive either elamipretide 4 mg, elamipretide 40 mg, or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The placebo for this study was provided as a sterile solution in matching sterile glass vials, which was composed of the excipients used to manufacture the IMP elamipretide without the active drug substance. The placebo was handled and administered identically as active drug. Subjects randomized to placebo received an injection containing either 1 mL or 0.1 mL of sterile solution to match the two volumes administered in the active arm.

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 an injection containing either 1 mL or 0.1 mL of sterile solution to match the two volumes administered in the active arm.

Arm title	4 mg elamipretide
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Arm description:

0.1 of elamipretide 40 mg/ml via single daily subcutaneous injection

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:

A single daily subcutaneous injection containing 0.1 mL of elamipretide 40 mg/ml.

Arm title	40 mg elamipretide
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Arm description:

1 ml of elamipretide 40 mg/ml via single daily subcutaneous injection

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:

A single daily subcutaneous injection containing 1 ml of elamipretide 40 mg/ml

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Day 1 (part of Period 2) was used for the baseline calculations.

Number of subjects in period 2	Placebo	4 mg elamipretide	40 mg elamipretide
Started	24	22	25
Completed	24	22	25

Period 3

Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
Arm description: Not applicable	
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: Not applicable	
Arm title	4 mg elamipretide
Arm description: Not applicable	
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: Not applicable	
Arm title	40 mg elamipretide
Arm description: Not applicable	
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: Not applicable	

Number of subjects in period 3	Placebo	4 mg elamipretide	40 mg elamipretide
Started	24	22	25
Completed	24	22	25

Baseline characteristics

Reporting groups

Reporting group title	Treatment
Reporting group description:	
Overall, 54 subjects (76.1%) were male and 17 subjects (23.9%) were female; the ratio of male to female subjects was different in all treatment groups. All subjects in the study were White and 37 subjects (52.1%) were \geq 65 years of age. Mean (SD) age was 64.8 years (9.83) years and mean (SD) weight was 86.72 (18.97) kg	

Reporting group values	Treatment	Total	
Number of subjects	71	71	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	34	
From 65-84 years	37	37	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	64.8		
standard deviation	\pm 9.83	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	54	54	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	Not applicable
Reporting group title	4 mg elamipretide
Reporting group description:	Not applicable
Reporting group title	40 mg elamipretide
Reporting group description:	Not applicable
Reporting group title	Placebo
Reporting group description:	The placebo for this study was provided as a sterile solution in matching sterile glass vials, which was composed of the excipients used to manufacture the IMP elamipretide without the active drug substance. The placebo was handled and administered identically as active drug. Subjects randomized to placebo received an injection containing either 1 mL or 0.1 mL of sterile solution to match the two volumes administered in the active arm.
Reporting group title	4 mg elamipretide
Reporting group description:	0.1 of elamipretide 40 mg/ml via single daily subcutaneous injection
Reporting group title	40 mg elamipretide
Reporting group description:	1 ml of elamipretide 40 mg/ml via single daily subcutaneous injection
Reporting group title	Placebo
Reporting group description:	Not applicable
Reporting group title	4 mg elamipretide
Reporting group description:	Not applicable
Reporting group title	40 mg elamipretide
Reporting group description:	Not applicable

Primary: Change from Baseline in Left Ventricular End Systolic Volume assessed by cardiac Magnetic Resonance Imaging (MRI)

End point title	Change from Baseline in Left Ventricular End Systolic Volume assessed by cardiac Magnetic Resonance Imaging (MRI)
End point description:	
End point type	Primary
End point timeframe:	4 weeks

End point values	Placebo	4 mg elamipretide	40 mg elamipretide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	22	24	
Units: mL				
arithmetic mean (standard deviation)	-3.8 (± 5.85)	-4.4 (± 6.50)	-1.2 (± 9.04)	

Statistical analyses

Statistical analysis title	ITT set analysis for efficacy assessment
Comparison groups	Placebo v 4 mg elamipretide v 40 mg elamipretide
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	2-sided, Hochberg's adjustment

Adverse events

Adverse events information

Timeframe for reporting adverse events:

20 June 2016 - 12 October 2017

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	4 mg elamipretide
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Reporting group description: -

Reporting group title	40 mg elamipretide
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Reporting group description: -

Serious adverse events	Placebo	4 mg elamipretide	40 mg elamipretide
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 22 (0.00%)	1 / 25 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Vestibular disorder			
subjects affected / exposed	0 / 24 (0.00%)	0 / 22 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	4 mg elamipretide	40 mg elamipretide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 24 (33.33%)	4 / 22 (18.18%)	12 / 25 (48.00%)
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 22 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Eosinophil count increased			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Troponin T increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Vascular disorders			
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Hypertension subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Hypotension subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 22 (4.55%) 1	1 / 25 (4.00%) 1
Headache subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Somnolence subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	2 / 22 (9.09%) 2	1 / 25 (4.00%) 1
Injection site erythema subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Injection site haemorrhage			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Injection site induration subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Injection site mass subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Injection site pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Productive cough			

subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Anxiety			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Haematuria			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Renal impairment			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Musculoskeletal pain			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Pain in extremity			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 22 (4.55%) 1	2 / 25 (8.00%) 2
Gastroenteritis viral			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0

Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Metabolism and nutrition disorders			
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Gout subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 22 (0.00%) 0	0 / 25 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 25 (4.00%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2016	Hyponatremia defined as sodium (Na+) level <125 mEq/L (This change was made and submitted only for UK)
01 December 2016	<ul style="list-style-type: none">• Inclusion criteria for known history of chronic ischemic or non-ischemic cardiomyopathy of at least 6 months duration from the time of the initial diagnosis was updated to include addition of signs and symptoms consistent with heart failure.• Inclusion criteria for LVEF was changed from $\leq 35\%$ to $\leq 40\%$ by 2-D echocardiography at Screening.• Exclusion criteria for subjects receiving treatment with therapeutic doses of anticoagulants was updated to include Vitamin K antagonists as well.• Exploratory endpoints was updated to include change in Borg dyspnea scale.• Week 1 visit was updated that on Days 1 through 3, subjects had to return to the site for the administration of IMP as well as the assessment of ISRs.• Respiratory rate recording was included for the tests to be done before and after the 6MWT.
21 March 2017	<ul style="list-style-type: none">• Methodology section was updated to include 70 subjects (at least 22 subjects in each group) for randomization, in 1:1:1 ratio, to receive either placebo, 4 mg elamipretide, or 40 mg elamipretide once daily for 28 consecutive days.• The number of subjects to be randomized was increased from 45 subjects to 70 subjects. As the initial sample size of 45 subjects was based on the assumption that a sample size of 15 subjects per treatment group provided 90% power to detect 8 mL difference between treatment groups in LV ESV, as measured by MRI, assuming a SD of 6.5 mL. A revised estimate of the SD, based on a review of blinded LV ESV data from the first 11 subjects who completed treatment, suggested it may ultimately be as high as 9.4 mL. Accordingly, the sample size was increased to around 22 subjects per treatment group, which provided 80% power to detect the aforementioned 8 mL difference between treatment groups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported