Clinical trial results:
A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients with Moderate to Severe Obesity

Summary

EudraCT number	2018-004058-11
Trial protocol	FR ES GB
Global end of trial date	08 March 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	RM-493-023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03746522
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rhythm Pharmaceuticals, Inc.
Sponsor organisation address	222 Berkeley Street, Boston, United States, MA 02116
Public contact	Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.com
Scientific contact	Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 2021
Global end of trial reached?	Yes
Global end of trial date	08 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a trial with 2 parts: a randomised, double-blind, placebo-controlled, 14-week, double-blind treatment period followed by a 52-week open-label treatment period (total treatment period up to 66 weeks).
The main objective was to assess the effect of setmelanotide on the proportion of patients (>=12 years of age at baseline) treated with setmelanotide for approximately (~) 52 weeks who achieve a clinically meaningful reduction from baseline (ie, >=10%) in body weight.

Protection of trial subjects:

The IRB/IEC reviewed all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study was only conducted at sites where IRB/IEC approval had been obtained. This study was conducted in accordance with:

• Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
• The International Council for Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]
• Applicable laws and regulatory requirements.

After the study had been fully explained, written informed consent was obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent complied with ICH-GCP and all applicable regulatory requirement(s).

Background therapy:

Medications approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) were not allowed within 3 months of randomization and were prohibited during the study.

Glucagon-like peptide-1 (GLP-1) receptor agonists were permitted up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) it was not prescribed for the treatment of obesity, (2) the dose had been stable for at least 3 months prior to randomization, (3) the patient had not experienced weight loss during the previous 3 months, and (4) the patient intended to keep the dose stable throughout the course of the study.

Other medications that could theoretically cause weight loss (e.g., stimulants) were allowed so long as the patient (1) had used them at a stable dose for at least 3 months prior to randomization, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable through the course of the study.

All concomitant medications were to be kept at a stable dose throughout the course of the study, unless a dose change was necessary to treat an adverse event (AE).

Evidence for comparator:

This was a placebo controlled trial for the first 14 weeks only. Therafter, subjects were treated open-label with setmelanotide only, with no comparator group.

Actual start date of recruitment	23 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 5
Worldwide total number of subjects	52
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)	11
Adolescents (12-17 years)	16
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period started on 23 November 2018. The last patient last visit was on 08 March 2021. Patients were recruited in the United States, Canada, France, Spain, and the United Kingdom.

Pre-assignment

Screening details:

After obtaining informed consent, potential patients were screened to determine study eligibility. The screening period lasted up to 3 weeks prior to randomisation.

Period 1

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

Blinding implementation details:

Eligible patients were randomised via an interactive website response system. Patients were randomised patients in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive setmelanotide or placebo for the first 14 weeks of the study. For the double-blind period, placebo and setmelanotide were identical in appearance and were supplied in identical packaging. Thereafter, all patients were treated with open-label setmelanotide.

Arms

Are arms mutually exclusive?	No
Arm title	All treated patients

Arm description:

All patients were treated with setmelanotide in this study.

The first 14 weeks of the study was a double-blind treatment period with patients randomised to setmelanotide or placebo. Thereafter, setmelanotide was administered open-label in all patients.

Patients randomised to setmelanotide were treated for up to 66 weeks with setmelanotide (14 weeks double-blind, followed by 52 weeks open-label).
Patients randomised to placebo were treated with placebo (matching setmelanotide) for 14 weeks followed by open-label setmelanotide for up to 52 weeks.

Dose escalations at the start of the double-blind and open-label treatment periods are described below.

A total of 38 patients (32 BBS patients and 6 AS patients) comprised the pivotal cohort.

Arm type	All treated patients
Investigational medicinal product name	Setmelanotide (with or without placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage by age group was as follows, including a dose escalation planned for the start of double-blind treatment (Weeks 1 and 2) and again at the start of open-label treatment to maintain the blind (Weeks 15 and 16).

Setmelanotide
Patients aged >=16 years:
Week 1, 2.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide
Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide
Patients aged <16 years:
Week 1, 1.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide
Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Placebo
All patients randomised to placebo (regardless of age group) were treated with placebo for Weeks 1-14. Thereafter, setmelanotide dosing was open-label, as detailed above by age group, for Weeks 15 to 66.

Arm title	Setmelanotide; double-blind period

Arm description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with setmelanotide.

Arm type	Experimental
Investigational medicinal product name	Setmelanotide (with or without placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage by age group was as follows, including a dose escalation planned for the start of double-blind treatment (Weeks 1 and 2) and again at the start of open-label treatment to maintain the blind (Weeks 15 and 16).

Setmelanotide
Patients aged >=16 years:
Week 1, 2.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide
Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide
Patients aged <16 years:
Week 1, 1.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide
Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Placebo
All patients randomised to placebo (regardless of age group) were treated with placebo for Weeks 1-14. Thereafter, setmelanotide dosing was open-label, as detailed above by age group, for Weeks 15 to 66.

Arm title	Placebo; double-blind period

Arm description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with placebo. At the end of the double-blind period these patients continued treatment with setmelanotide.
Patients aged >=16 years:
Week 1-14, placebo
Week 15, 2.0 mg setmelanotide; Week 16 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide
Patients aged <16 years:
Week 1-14, placebo
Week 15, 1.0 mg setmelanotide; Week 16, 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

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:

Patients randomised to placebo received placebo under double-blind conditions for 14 weeks followed by active treatment with setmelanotide (open-label) until the end of the study. Dose escalation occurred over the first 2 weeks of the double-blind period and again at the start of the open-label period to maintain the blind.

Patients aged >=16 years:
Week 1-14, placebo
Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide
Patients aged <16 years:

Week 1-14, placebo
Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Number of subjects in period 1	All treated patients	Setmelanotide; double-blind period	Placebo; double-blind period
Started	52	27	25
Completed	39	22	17
Not completed	13	5	8
Transfer to extension study	2	-	-
Consent withdrawn by subject	3	3	2
Adverse event, non-fatal	6	2	3
Lost to follow-up	2	-	1
Discontinued during double-blind period	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
All treated patients, including patients treated with placebo during the double-blind placebo-controlled period (first 14 weeks of study).	

Reporting group values	Baseline	Total	
Number of subjects	52	52	
Age categorical			
Units: Subjects			
Children (2-11 years)	11	11	
Adolescents (12-17 years)	16	16	
Adults (18-64 years)	25	25	
Age continuous			
Units: years			
arithmetic mean	19.5		
standard deviation	± 10.96	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	21	21	
Underlying condition			
Patients with Bardet-Biedl Syndrome (BBS) or Alström Syndrome (AS) condition were eligible to participate.			
Units: Subjects			
BBS	44	44	
AS	8	8	
Body Mass Index (kg/m2)			
Units: kg/m2			
arithmetic mean	41.78		
standard deviation	± 11.116	-	
Weight			
Units: kg			
arithmetic mean	107.78		
standard deviation	± 34.582	-	

End points

End points reporting groups

Reporting group title	All treated patients

Reporting group description:

All patients were treated with setmelanotide in this study.

The first 14 weeks of the study was a double-blind treatment period with patients randomised to setmelanotide or placebo. Thereafter, setmelanotide was administered open-label in all patients.

Patients randomised to setmelanotide were treated for up to 66 weeks with setmelanotide (14 weeks double-blind, followed by 52 weeks open-label).
Patients randomised to placebo were treated with placebo (matching setmelanotide) for 14 weeks followed by open-label setmelanotide for up to 52 weeks.

Dose escalations at the start of the double-blind and open-label treatment periods are described below.

A total of 38 patients (32 BBS patients and 6 AS patients) comprised the pivotal cohort.

Reporting group title	Setmelanotide; double-blind period

Reporting group description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with setmelanotide.

Reporting group title	Placebo; double-blind period

Reporting group description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with placebo. At the end of the double-blind period these patients continued treatment with setmelanotide.
Patients aged >=16 years:
Week 1-14, placebo
Week 15, 2.0 mg setmelanotide; Week 16 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide
Patients aged <16 years:
Week 1-14, placebo
Week 15, 1.0 mg setmelanotide; Week 16, 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Primary: Body weight change

End point title	Body weight change[1][2]

End point description:

The primary endpoint was the proportion of pivotal patients ≥12 years old who met the ≥10% weight loss threshold from baseline (i.e., responders) after approximately 1 year of treatment with setmelanotide. This analysis was performed on the FAS population, with patients who received any study drug and at least one baseline assessment. Weight was measured in triplicate at each visit and mean values analysed. The estimated proportion of pivotal patients ≥12 years of age who achieved a ≥10% reduction in body weight was compared to a historical control rate of 10%.

This was not a comparative analysis. Binomial proportions for 100 imputed datasets and outcomes were combined using Rubin's Rule to provide an overall estimate. A 1-sided 0.025 significance level was used based on the small sample size (due to rarity of the disease).
Results of statistical analysis: point estimate: 32.3% (95% CI 16.7, 51.4), p=0.0006, indicating primary efficacy endpoint was met.

End point type	Primary

End point timeframe:

Baseline to 1 year on active treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis of the primary endpoint was based upon comparison with historical

data at the end of the open-label treatment period. Details of the statistical analysis are included with the endpoint description.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No comparisons of efficacy for the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight

End point title	Percentage change in body weight[3]

End point description:

Mean percentage of body weight change (kg) from baseline in pivotal patients ≥12 years old after 1 year of treatment with setmelanotide within a single group of patients based on the FAS.

Analyses were based on a one-sample t-test for each of the 100 imputed datasets and assuming a mean percent change from baseline in body weight of zero. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CIs. This was evaluated at a 1-sided, 0.025 significance level.

Results of statistical analysis: mean change after 52 weeks of treatment: -5.21% (95% CI -9.17, -3.77), p=0.0005, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

Change from baseline to Week 52

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percent				
arithmetic mean (standard deviation)	-5.21 (± 7.895)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score

End point title	Change in hunger score[4]

End point description:

Evaluation of the mean percent change in hunger scores (weekly average hunger score of the daily most/worst hunger score over 24 hours) in pivotal patients ≥12 years of age at the end of approximately 1 year of treatment within a single group of patients.

Analyses were based on a one-sample t-test for each of the 100 imputed datasets with an assumed mean percent change from baseline in weekly average of daily hunger scores of zero. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CIs. This was evaluated at a 1-sided, 0.025 significance level.

Results of statistical analysis: mean change after 52 weeks: -30.91% (95% CI -44.09, -17.73), p<0.0001, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

From baseline to Week 52

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent				
arithmetic mean (standard deviation)	-30.91 (± 24.733)			

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in daily hunger score

End point title	Improvement in daily hunger score[5]

End point description:

The proportion of pivotal patients ≥12 years of age in the FAS population who achieve a ≥25% improvement from baseline in the weekly average of the daily hunger score after ~52 weeks of treatment was analyzed similarly to the primary efficacy endpoint (described above). Prior to analysis, daily hunger scores for each of the 3 hunger assessments (worst/most) were averaged separately by week.

Results of statistical analysis: point estimate: 62.5% (95% CI 35.4, 84.8); p<0.0001.

End point type	Secondary

End point timeframe:

From baseline to Week 52.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Subjects	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events after the start of study drug administration were treatment-emergent (TEAEs).
Total duration of treatment (randomised to setmelanotide/placebo): 66 weeks setmelanotide /14 weeks placebo plus 52 weeks setmelanotide.

Adverse event reporting additional description:

TEAEs are presented for all patients who received at least 1 study drug dose. Note, 25 of the 52 treated patients were treated with placebo in the 14-week double-blind period before starting setmelanotide.
NOTE: TEAEs in the 14-week double-blind period include ONLY those TEAEs with an onset during that 14-week period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	All treated patients to end of follow-up

Reporting group description:

All patients treated with study drug. Total duration of treatment (randomised to setmelanotide/placebo): up to 66 weeks setmelanotide /14 weeks placebo plus up to 52 weeks setmelanotide.

Reporting group title	Setmelanotide during 14-week double-blind period only

Reporting group description:

Patients randomised to setmelanotide for the 14-week double-blind period.

Reporting group title	Placebo during 14-week double-blind period only

Reporting group description:

Patients randomised to placebo for the 14-week double-blind period.

Serious adverse events	All treated patients to end of follow-up	Setmelanotide during 14-week double-blind period only	Placebo during 14-week double-blind period only
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	2 / 25 (8.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 52 (1.92%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness			
subjects affected / exposed	1 / 52 (1.92%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All treated patients to end of follow-up	Setmelanotide during 14-week double-blind period only	Placebo during 14-week double-blind period only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 52 (100.00%)	26 / 27 (96.30%)	24 / 25 (96.00%)
Investigations			
High density lipoprotein decreased			
subjects affected / exposed	4 / 52 (7.69%)	4 / 27 (14.81%)	0 / 25 (0.00%)
occurrences (all)	4	4	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	6 / 52 (11.54%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences (all)	7	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 52 (23.08%)	1 / 27 (3.70%)	6 / 25 (24.00%)
occurrences (all)	51	20	7
Dizziness			
subjects affected / exposed	4 / 52 (7.69%)	1 / 27 (3.70%)	2 / 25 (8.00%)
occurrences (all)	4	1	2
General disorders and administration			

site conditions			
Injection site erythema			
subjects affected / exposed	26 / 52 (50.00%)	12 / 27 (44.44%)	11 / 25 (44.00%)
occurrences (all)	35	17	12
Injection site pruritus			
subjects affected / exposed	20 / 52 (38.46%)	8 / 27 (29.63%)	9 / 25 (36.00%)
occurrences (all)	26	11	9
Injection site pain			
subjects affected / exposed	14 / 52 (26.92%)	3 / 27 (11.11%)	8 / 25 (32.00%)
occurrences (all)	19	4	10
Injection site bruising			
subjects affected / exposed	18 / 52 (34.62%)	6 / 27 (22.22%)	9 / 25 (36.00%)
occurrences (all)	18	6	9
Injection site induration			
subjects affected / exposed	14 / 52 (26.92%)	6 / 27 (22.22%)	4 / 25 (16.00%)
occurrences (all)	17	6	4
Fatigue			
subjects affected / exposed	6 / 52 (11.54%)	1 / 27 (3.70%)	2 / 25 (8.00%)
occurrences (all)	6	1	2
Injection site haemorrhage			
subjects affected / exposed	6 / 52 (11.54%)	3 / 27 (11.11%)	2 / 25 (8.00%)
occurrences (all)	6	3	2
Injection site oedema			
subjects affected / exposed	6 / 52 (11.54%)	2 / 27 (7.41%)	1 / 25 (4.00%)
occurrences (all)	6	2	1
Injection site reaction			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	2 / 25 (8.00%)
occurrences (all)	4	2	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 52 (36.54%)	7 / 27 (25.93%)	6 / 25 (24.00%)
occurrences (all)	25	7	7
Vomiting			
subjects affected / exposed	14 / 52 (26.92%)	7 / 27 (25.93%)	0 / 25 (0.00%)
occurrences (all)	18	9	0
Diarrhoea			

subjects affected / exposed	10 / 52 (19.23%)	2 / 27 (7.41%)	1 / 25 (4.00%)
occurrences (all)	12	3	1
Abdominal pain upper			
subjects affected / exposed	4 / 52 (7.69%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	6	0	1
Abdominal pain			
subjects affected / exposed	4 / 52 (7.69%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	4	0	1
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	5 / 52 (9.62%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences (all)	5	1	0
Menorrhagia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	3	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 52 (9.62%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	5	0	2
Nasal congestion			
subjects affected / exposed	3 / 52 (5.77%)	3 / 27 (11.11%)	0 / 25 (0.00%)
occurrences (all)	3	3	0
Rhinorrhoea			
subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	3	0	2
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	33 / 52 (63.46%)	17 / 27 (62.96%)	0 / 25 (0.00%)
occurrences (all)	53	24	0
Acne			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Dermatitis atopic			
subjects affected / exposed	3 / 52 (5.77%)	2 / 27 (7.41%)	0 / 25 (0.00%)
occurrences (all)	3	2	0
Dry skin			

subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	3	0	2
Skin striae			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 52 (9.62%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	5	0	1
Arthralgia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 52 (7.69%)	2 / 27 (7.41%)	1 / 25 (4.00%)
occurrences (all)	4	2	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences (all)	4	1	0
Urinary tract infection			
subjects affected / exposed	4 / 52 (7.69%)	1 / 27 (3.70%)	1 / 25 (4.00%)
occurrences (all)	4	1	1
Ear infection			
subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	1 / 25 (4.00%)
occurrences (all)	3	0	1
Pharyngitis streptococcal			
subjects affected / exposed	3 / 52 (5.77%)	0 / 27 (0.00%)	2 / 25 (8.00%)
occurrences (all)	3	0	2
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 27 (3.70%)	0 / 25 (0.00%)
occurrences (all)	3	1	0

Glucose tolerance impaired subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2018	The following substantive changes were introduced: • Updated the packaging description. • Optional sleep study timepoint was added to V6. • Removed the requirement for electronic storage of ECGs, recording of ECGs in triplicate, and for use of equipment capable of transmitting to a central reader. • Clarified that the optional sleep study would be performed as a standard overnight sleep study.
04 February 2019	•Synopsis updated to clarify ages of enrolment •Inclusion #2 updated to clarify the ages of enrolment •Clarification of Exclusion #2 allowable medications and timeframe •Exclusion #4 re-written to remove only DSM-V disorders •Exclusion # 7 added to exclude patients with HbA1c >9.0 at screening •Added glomerular filtration rate •Exclusion #14 added to exclude patients previously treated with setmelanotide •Exclusion #17 added to exclude patients with first degree relatives enrolled within the past 4 months •Clarification that the Investigator had direct access to the system to unblind the treatment in case of emergency •The prohibited medication section was revised •The Screening Period updated to a minimum of 1 week with at least 4 days completed in the electronic hunger diary •Schedule of Assessments updated to add the HbA1c testing noted above •The list of biomarkers to be tested for was revised (some were removed) •Extended the screening period •Table 2 footnote 8 updated to describe a minimum of 1 week of screening and to require hunger diary completion on 4 out of 7 days prior to randomization •Text removed to clarify genetic testing samples would not be used for any other purpose •Clarified that Global Hunger to be completed during visits and the Daily Hunger to be completed electronically each day •Text added to state the PWS-SEQ was to be used in place of the Global Hunger questions in patients with impaired cognitive function •Text added to state the neurocognition tests WAIS-IV or WISC-V could be waived after discussion with the sponsor •Clarified the collection of samples for ACTH and 24-hour urine •Added that archive samples would be discarded at the end of the study •Text added to further define unlikely AE relationship •Text added to describe analysis options of incomplete data •Cockcroft Gault Equation changed to the Modification of Diet in Renal Disease Study equation for patients ≥18 or the Bedside Schwartz for patients <18

16 August 2020	The following changes were introduced: • Key secondary objectives updated to reflect a mean percent change from baseline in the weekly average of the daily hunger score. Key Secondary Objectives #1 and #4 were moved to Exploratory. Key Secondary Objective #2 was re-written to specify baseline body weight. Other Secondary Objective #2 was moved to Exploratory. • Key Secondary Endpoints # 1 and #3 were removed (moved to Exploratory). Added Exploratory Endpoint describing the proportion of patients who achieve an improvement in daily hunger score. • Updated to clarify the number of patients enrolled in the Pivotal and Supplemental cohorts. • Updated Inclusion Criteria #2 to specify age at time of first dose. • The Statistical Considerations section of the Synopsis and Section 8, Data Analysis/Statistical Procedures were revised. • The Clinical Overview section was updated with current exposure numbers and entire Clinical Safety section replaced providing updated TEAEs and SAE incidence to align with the annual Investigator Brochure update. • Text was added to allow Supplemental patients to roll into the extension study starting at Visit 8 or later. • Flexibility added to visit schedule windows upon sponsor approval to accommodate difficulty in scheduling due to COVID-19, holidays, and other logistical issue. • Schedule of Assessments was updated to make WISC-V/WAIS-IV optional based on investigator discretion. • Schedule of Assessments – removed Nutritional counselling and monitoring from V 2, 4, 6, 8, 10, and 12. • Schedule of Assessments bullet 11 was removed and 6.5.8 Measures of Insulin Sensitivity/Resistance OGTT was removed. • Updated PK profile blood draw time point preferences to pre-dose 4, 6, and 8 hours. Tubes provided in lab kits collect ~6 mL alloallowing for 2 aliquots. • Clarified that study medication should be taken after obtaining vital signs.
09 September 2020	The following changes were introduced: • Change and percent change in OGTT was removed from the Exploratory Endpoints (Already done for Ver 2.1 Marshfield Clinic only). • Additional clarity was added regarding the timing of dose escalation, the associated visit or phone call, and the visit windows for these days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported