Clinical trial results:
Title: A Phase 3 Multi-Center, One-Year, Open-Label study of Setmelanotide in Pediatric Patients Aged 2 to <6 years of age with Rare Genetic Causes of Obesity.

Trial design: This was an open-label study to evaluate the efficacy, safety, and tolerability of setmelanotide in paediatric patients with rare genetic causes of obesity (biallelic mutations of the POMC, PCSK1, or LEPR [PPL] genes or with Bardet-Biedl syndrome [BBS]). Eligible patients began treatment with setmelanotide at a dose of 0.5 mg/day. The dose was increased by increments of 0.5 mg every 2 weeks, if tolerated, at dose escalation visits (Weeks 2, 4, and 6). The maximum dose level for patients who weighed <20 kg, 20 to <30 kg, 30 to <40 kg, and >=40 kg was 0.5, 1.0, 1.5, and 2.0 mg once daily (QD), respectively. In total, 12 patients, aged 2 to <6 years were enrolled in the study.

Screening assessments included medical history, abbreviated physical exam, comprehensive skin examination, laboratory tests, blood pressure.

If a patient’s weight decreased to less than 15 kg during the study, the Investigator and sponsor jointly determined whether a patient's dose should change or be discontinued temporarily or permanently. A dose reduction to a minimum of 0.25 mg QD was allowed in such cases, or in case of tolerability concerns.

Study assessments were performed at study visits approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52. The primary objective was to evaluate the effect of setmelanotide on weight-related parameters in paediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the PPL genes or (2) BBS.

Overall, the median duration of treatment was 52.2 weeks (range: 7.1 to 54.9 weeks) and was similar in both groups of patients.

Summary

EudraCT number	2021-004167-27
Trial protocol	NL ES
Global end of trial date	08 November 2024

Results information

Result version number	v1 (current)
This version publication date	06 December 2024
First version publication date	06 December 2024

Trial information

Trial identification

Sponsor protocol code	RM-493-033

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Rhythm Pharmaceuticals, Inc
Sponsor organisation address	222 Berkeley Street, 12th Floor, Boston, United States, MA 02116
Public contact	Clinical Trial Associate, Rhythm Pharmaceuticals, Inc., 01 857-264-4280, clinicaltrials@rhythmtx.com
Scientific contact	Clinical Trial Associate, Rhythm Pharmaceuticals, Inc., 01 857-264-4280, clinicaltrials@rhythmtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002209-PIP01-17
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	04 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2024
Global end of trial reached?	Yes
Global end of trial date	08 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of setmelanotide on weight in pediatric patients aged 2 to <6 years with obesity due to either (1) biallelic variants of the POMC, PCSK1 or LEPR genes or (2) Bardet-Biedl Syndrome (BBS) by determining if they meet a “responder” definition for change in body weight.

Protection of trial subjects:

An Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved the final study protocol, including the final version of the informed consent and any changes to the informed consent. IRB or IEC approval was submitted to the Sponsor before any patient was enrolled in the study. Any amendments to the protocol were also approved by the IRB or IEC upon receipt of amendments and annually, as local regulations required in accordance with local requirements. In addition, the IRB or IEC approved all advertising used to recruit patients for the study.

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

The Investigator(s) at each site ensured that the patient and their legal guardian were given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study and adequate opportunity to ask questions. The parent/legal guardian(s) signed and dated consent and assent were obtained before any study procedures were conducted. Patients and their legal guardian(s) were informed that they were free to discontinue from the study at any time.

Background therapy:

All medication or vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) in use at the time of enrolment or used during the study were recorded as prior or concomitant medications, as appropriate, along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The dose of concomitant medications used during the study was not to be changed and new concomitant medications were not to be started during the study, unless necessary to treat an AE.

Evidence for comparator: -

Actual start date of recruitment	08 March 2022
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	Australia: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	12
EEA total number of subjects	2

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)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited 7 paediatric patients with biallelic mutations of the POMC, PCSK1, or LEPR genes (collectively referred to as PPL) and 5 paediatric patients with Bardet Biedl Syndrome (BBS) in Australia, Spain, United Kingdom, and the United States from 02 Mar 2022. The last patient last visit was 18 Sep 2023.

Pre-assignment

Screening details:

Screening assessments included medical history, abbreviated physical exam, comprehensive skin examination, laboratory tests, and blood pressure.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Paediatric patients with PPL

Arm description:

Paediatric patients with biallelic mutations of the POMC, PCSK1, or LEPR genes.

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

Dosage and administration details:

All eligible patients began treatment with setmelanotide at a dose of 0.5 mg per day. The setmelanotide dose was increased by increments of 0.5 mg every 2 weeks, if tolerated, at the dose escalation visits (Weeks 2, 4, and 6). At each visit, the decision to escalate the dose was based on tolerability and health status.

The maximum dose level in this study for patients who weigh <20 kg, 20 to <30 kg, 30 to <40 kg, and ≥40 kg was 0.5, 1.0, 1.5, and 2.0 mg QD, respectively.

Height and weight were monitored closely during the study. If a patient’s weight decreased to below 15 kg during the study, a discussion regarding possible dose reduction occurred. A dose reduction to a minimum of 0.25 mg QD was allowed in such cases, or in case of tolerability concerns. The dose continued to be evaluated and adjusted, at the discretion of the investigator, as long as the daily dose was kept between 0.25 and 2.0 mg QD and did not exceed the maximum dose for the patient's weight.

Arm title	Paediatric patients with BBS

Arm description:

Paediatric patients with Bardet Biedl Syndrome.

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

Dosage and administration details:

All eligible patients began treatment with setmelanotide at a dose of 0.5 mg per day. The setmelanotide dose was increased by increments of 0.5 mg every 2 weeks, if tolerated, at the dose escalation visits (Weeks 2, 4, and 6). At each visit, the decision to escalate the dose was based on tolerability and health status.

The maximum dose level in this study for patients who weigh <20 kg, 20 to <30 kg, 30 to <40 kg, and ≥40 kg was 0.5, 1.0, 1.5, and 2.0 mg QD, respectively.

Height and weight were monitored closely during the study. If a patient’s weight decreased to below 15 kg during the study, a discussion regarding possible dose reduction occurred. A dose reduction to a minimum of 0.25 mg QD was allowed in such cases, or in case of tolerability concerns. The dose continued to be evaluated and adjusted, at the discretion of the investigator, as long as the daily dose was kept between 0.25 and 2.0 mg QD and did not exceed the maximum dose for the patient's weight.

Number of subjects in period 1	Paediatric patients with PPL	Paediatric patients with BBS
Started	7	5
Completed	6	5
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Paediatric patients with PPL
Reporting group description:	
Paediatric patients with biallelic mutations of the POMC, PCSK1, or LEPR genes.	
Reporting group title	Paediatric patients with BBS
Reporting group description:	
Paediatric patients with Bardet Biedl Syndrome.	

Reporting group values	Paediatric patients with PPL	Paediatric patients with BBS	Total
Number of subjects	7	5	12
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	7	5	12
Adolescents (12-17 years)	0	0	0
Age continuous			
Units: years			
arithmetic mean	3.4	3.8	
standard deviation	± 0.53	± 1.30	-
Gender categorical			
Units: Subjects			
Female	2	3	5
Male	5	2	7
Gene Type			
The efficacy, safety, and tolerability of setmelanotide is being studied in paediatric patients 2 to <6 years of age with variants in POMC, PCSK1, or LEPR (PPL) genes or with BBS. This characteristic shows which rare genetic cause of obesity each group had.			
Units: Subjects			
POMC	3	0	3
PCSK1	0	0	0
LEPR	4	0	4
BBS	0	5	5
Weight at baseline			
The most recent weight measurement prior to the first administration of study drug.			
Units: kilogram(s)			
arithmetic mean	44.933	28.300	
standard deviation	± 12.0142	± 13.0434	-
Height at baseline			
The most recent height measurement prior to the first administration of study drug.			
Units: centimetre			
arithmetic mean	114.210	106.740	
standard deviation	± 9.3718	± 17.1072	-
BMI at baseline			
The most recent body mass index (BMI) measurement prior to the first administration of study drug.			
Units: kg/m2			
arithmetic mean	34.347	23.716	

standard deviation	± 7.0673	± 3.5184	-
Waist circumference at baseline			
The most recent waist circumference measurement prior to the first administration of study drug.			
Units: centimetre			
arithmetic mean	89.014	66.213	
standard deviation	± 14.3713	± 13.2926	-
BMI Z-score at baseline			
BMI Z-score is a measure of how many standard deviations a child or young person's BMI is above or below the average BMI for their age and gender.			
Units: Z-score			
arithmetic mean	10.749	4.233	
standard deviation	± 3.8400	± 1.0742	-

End points

End points reporting groups

Reporting group title	Paediatric patients with PPL
Reporting group description:	
Paediatric patients with biallelic mutations of the POMC, PCSK1, or LEPR genes.	
Reporting group title	Paediatric patients with BBS
Reporting group description:	
Paediatric patients with Bardet Biedl Syndrome.	

Primary: Proportion of Patients who Achieve a Decrease in BMI Z-Score ≥0.2 from Baseline to Week 52

End point title	Proportion of Patients who Achieve a Decrease in BMI Z-Score ≥0.2 from Baseline to Week 52[1]

End point description:

The proportion of patients who met a "responder" definition, defined as a decrease from baseline to 52 weeks in the patient's BMI Z-score of ≥0.2. Baseline was defined as the most recent measurement prior to the first administration of study drug. Heights and weights were collected in triplicate at each visit. These were aggregated into one averaged value per visit prior to calculating the patient's BMI and BMI Z-score. BMI Z-scores are based on the World Health Organization's Child Growth Standards 2007. Two-sided 95% CI was calculated using the Clopper-Pearson Method.

End point type	Primary

End point timeframe:

From baseline to Week 52

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: This was not a comparator study. For the primary endpoint BMI Z-score, the Z-score represents how many SDs the individual's BMI is from the median BMI of the reference population. A "responder" was defined as a decrease from baseline to 52 weeks in the patient's BMI Z-score of ≥0.2. The proportion of responders and the corresponding 2-sided 95% CI using the Clopper-Pearson method were reported.

End point values	Paediatric patients with PPL	Paediatric patients with BBS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: percent				
number (confidence interval 95%)	85.7 (54.1 to 100)	80.0 (28.4 to 99.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Percent Change in BMI From Baseline to Week 52

End point title	Mean Percent Change in BMI From Baseline to Week 52[2]

End point description:

The mean percent change in BMI from baseline to Week 52. Baseline was defined as the most recent

measurement prior to the first administration of study drug. Heights and weights were collected in triplicates at each visit. These were aggregated into one averaged value per visit prior to calculating the patient's BMI. Two-sided 95% CI is calculated with Student's t-distribution.

End point type	Primary

End point timeframe:

From baseline to Week 52.

Notes:

[2] - 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: This was not a comparator study. For the analysis of mean percent change in BMI from baseline, percent changes in BMI from baseline over time were summarized using descriptive statistics.

End point values	Paediatric patients with PPL	Paediatric patients with BBS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: percent				
arithmetic mean (confidence interval 95%)	-25.597 (-37.66 to -13.54)	-9.719 (-20.69 to 1.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Absolute Change in BMI Z-score from Baseline to Week 52

End point title	Mean Absolute Change in BMI Z-score from Baseline to Week 52

End point description:

The mean change from baseline to Week 52 in BMI Z-score. Baseline is defined as the most recent measurement prior to the first administration of study drug. Heights and weights were collected in triplicates at each visit. These were aggregated into one averaged value per visit prior to calculating the patient's BMI and BMI Z-score. BMI Z-scores are based on the World Health Organization's Child Growth Standards 2007.

End point type	Secondary

End point timeframe:

From baseline to Week 52.

End point values	Paediatric patients with PPL	Paediatric patients with BBS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Z-score				
arithmetic mean (standard deviation)	-5.185 (± 1.8585)	-1.331 (± 1.2295)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Percent of the BMI 95th Percentile from Baseline to Week 52

End point title	Mean Change in Percent of the BMI 95th Percentile from Baseline to Week 52

End point description:

The mean change from baseline to Week 52 in the percent of the BMI 95th percentile. Baseline was defined as the most recent measurement prior to the first administration of study drug. Weights were collected in triplicates at each visit. These were aggregated into one averaged value per visit.

End point type	Secondary

End point timeframe:

From baseline to Week 52.

End point values	Paediatric patients with PPL	Paediatric patients with BBS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: percent				
arithmetic mean (standard deviation)	-47.595 (± 17.3280)	-14.462 (± 13.8571)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to Week 52	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1
Reporting groups	
Reporting group title	Overall Patients
Reporting group description: All patients from the PPL and BBS group.	

Serious adverse events	Overall Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	25		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Injection site bruising			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Injection site pruritus			

subjects affected / exposed	4 / 12 (33.33%)			
occurrences (all)	4			
Injection site discolouration				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	3			
Injection site erythema				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Fatigue				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Chest discomfort				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Gait disturbance				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Impaired healing				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Induration				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Injection site induration				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Injection site oedema				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Injection site pain				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Injection site urticaria				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Food allergy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Genital erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Increased upper airway secretion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Serum ferritin decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Skin abrasion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Sports injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Eye contusion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Head injury subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Humerus fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Immunisation reaction subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Radius fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin laceration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Tooth avulsion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Upper limb fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Change in seizure presentation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Eye disorders Eye ulcer subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ocular discomfort subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	7 / 12 (58.33%) 14		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Nausea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Anal erythema subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Breath odour subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Frequent bowel movements			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gingival hyperpigmentation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pigmentation lip			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	47		
Dermatitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Pityriasis rosea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Skin discolouration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Drug eruption			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Ephelides			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hand dermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nail pigmentation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Onychoclasis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin hypopigmentation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Limb discomfort			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Ear infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Otitis media			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Pharyngitis streptococcal			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
COVID-19			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pharyngotonsillitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Skin candida			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Acarodermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Conjunctivitis subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Gastrointestinal viral infection subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all) Polydipsia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2021	Version 1.1: • Body weight categories were established to determine the maximum daily dose based on the patient's body weight. • The exclusion criterion pertaining to inadequate hepatic function was added. • The statistical considerations were changed to align with the changes to the study objectives and endpoints . • Additional pharmacokinetic timepoints were added. • Text was updated to reflect the revised PK modeling. • For pediatric patients, the modified Schwartz equation will be used to calculate renal function (mL/min/1.73m2).
24 January 2022	Version 2.0: • Wording of the study objectives was edited to improve clarity and consistency between primary and secondary objectives and endpoints • The possibility to reduce the dose down to 0.25 mg was introduced in order to mitigate the risk of drug discontinuation, in case of tolerability/safety concerns. • The possibility for the Investigator to pause dose-escalation was further elaborated, to allow for dose adjustment which may enhance patient adherence to treatment and reaching of final maintenance dose level. • Sample size was expanded to allow enrollment of up to 15 patients to increase the chances to include patients with each of the genetic conditions. • The following inclusion criterion was added: – Symptoms or behaviors of hyperphagia at any time during the patient's life, as determined by the Investigator at screening. • The following exclusion criterion was added – Any other uncontrolled endocrine, metabolic or medical condition(s) known to impact body weight that could potentially interfere with interpretation of study results. • Wording of the study endpoints was edited to improve clarity and better reflect the descriptive nature of the endpoints, given the small sample size. • Benefit-risk text was edited to better reflect the importance of early treatment. • The approval status of setmelanotide was updated. • The following text pertaining to the Screening period was added: - A patient who did not meet one or more of the eligibility criteria was considered a screen failure. Any patient that was rescreened was required to have a new ICF signed by the parent or guardian. • Additional text was added for clarity in case of treatment discontinuation to highlight the importance of retaining patients in the study regardless of whether they discontinued study drug prematurely.

24 January 2022	Version 2.0 continued: • Allowed a home nurse to assist with injections if requested. • Weight-related history including growth charts since birth would be obtained and reported. • Protection from sun was advised. • Weight was to be measured at approximately the same time of day throughout the study. • Specified that the stadiometer was to be calibrated by site personnel on a daily basis prior to height assessment. • Specified that waist circumference was to be measured at approximately the same time of day throughout the study and according to the NHLBI criteria. • Text regarding the participation in the parent exit interview was added. • Text was added regarding blood sampling during site visits. • Weight-based maximal dose values were added in the overdose section. • Given the young age of the patient population, a provision was added that if PK profile could not be obtained for a given visit due to logistical challenges, the Investigator should at least obtain sample for trough PK (pre-dose). • Text added on conducting a clinical study during the global pandemic.
10 March 2022	• The required baseline body weight for inclusion in the study was decreased. • Clarified criteria to permit certain telephone visits. • The text concerning dose selection was modified to reflect the changes made to the study entry weight criterion.
05 December 2022	Version 4.0: • Provided dose escalation instructions in the event of a tolerability concern. • Included criteria for LTE eligibility and bridging visits to the LTE, if applicable; refined definition of study completion to account for patients who transition to the LTE or terminate early or withdraw. • Added a co-primary endpoint of percent change in BMI; removed revised co-primary endpoint from secondary endpoints. • Provided instructions to delineate the conditions that would necessitate patient referral to a mental health professional. • Specified that if there were logistical challenges collecting the 10- to 12-hour post-dose PK sample, the sample could have been collected at 8 hours post-dose. • Revised the language on approved indications in global regions. • Revised the Benefit/Risk section to reflect the totality of the setmelanotide program. • Added sections to describe the following assessments: Fitzpatrick scale and ADA sample collection.
22 June 2023	Version 5.0: • Removed dosing diary requirements during Bridging Visits • Removed optional caregiver exit interviews • Corrected the intention to collect PK trough instead of PK profile at the ETT Visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported