Clinical trial results:
An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function LEPR Genetic Mutation

Summary

EudraCT number	2017-002005-36
Trial protocol	DE FR NL GB
Global end of trial date	25 September 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	RM-493-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03287960
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)	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	24 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2020
Global end of trial reached?	Yes
Global end of trial date	25 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with LEPR deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment.

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. The protocol, investigator brochure (IB), informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents was provided to the IRB/IEC by the Investigator.

Although the study procedures and assessments required per protocol were classified as "No or Minimal Risk" (apart from DEXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age were included in the protocol.

Background therapy:

Unless concomitant medications were likely to present a strong potential safety concern, to allow as many as possible patients with this ultra-rare condition to participate in the study, patients were allowed chronic concomitant medications while participating in the study, including:

1) Growth hormone
2) Contraceptives
3) Hormone replacement therapy (female patients were permitted hormonal contraception as well as hormone replacement therapy)
4) Anti-hypertensives
5) Statins and other lipid-lowering therapies
6) Thyroxine or other thyroid supplements
7) Other medications commonly used in patients with obesity: endocrine therapies (e.g., estrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetic therapies including insulin); and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).
8) Except for low threshold drugs (i.e., anticonvulsants, digoxin, Coumadin, etc.), other medications were permitted if the patient was on a stable dose upon consultation with the Sponsor.

Female patients were allowed to use hormonal contraception as well as hormone replacement therapy. Medications that could impact the efficacy assessments during the study were prohibited.
Anorectic agents or drugs with anorexia as a non-rare side effect were prohibited for the duration of the study.

Evidence for comparator:

No active comparator was used in the study, but the study was powered based upon natural history data. There was a double-blind randomized withdrawal period which included 4 weeks placebo and 4 weeks active treatment.

Actual start date of recruitment	08 January 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: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	15
EEA total number of subjects	13

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)	1
Adolescents (12-17 years)	4
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged >= 6 years, with bi-allelic loss of function (LOF) LEPR genetic mutation conferring a severe obesity phenotype were eligible to participate.
If adult age ≥18 years, obesity with body mass index (BMI) ≥30 kg/m2; if child or adolescent, obesity with BMI ≥95th percentile for age (by gender) on growth chart assessment.

Pre-assignment

Screening details:

At screening, a blood sample was obtained for genotyping for mechanisms considered to be possibly related to the safety or efficacy response to the study medication (e.g., other obesity related genes). Complete physical, relevant bloodwork and other standard assessments were performed. All bloodwork was collected between Study Day -28 and -14.

Period 1

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

Blinding implementation details:

This was an open-label study with a dose titration period lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual’s therapeutic dose) followed by a further 10 weeks of open-label treatment at that dose. This was followed by an 8-week double-blind withdrawal period (4 weeks placebo and 4 weeks on setmelanotide; timing of each was randomly assigned) then continued treatment with setmelanotide to the end of 1-year's treatment (32 weeks open-label).

Arms

Arm title	All treated patients

Arm description:

All patients treated with setmelanotide, includes a combination of 11 patients enrolled in a 'pivotal cohort' and 4 patients in a 'supplemental' cohort. All patients had the LEPR genetic mutation.

Arm type	Experimental
Investigational medicinal product name	Setmelanotide
Investigational medicinal product code	RM-493-mPEG-DSPE
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Study patients were administered study drug by subcutaneous (SC) injection once daily (in the morning). The dose titration phase lasted up to 10 weeks with assessments every 2 weeks to determine if a dose should be increased. Once the patient’s therapeutic dose was reached, the same dose was administered throughout the remainder of the study.

Initial doses administered were 1.0 mg (adult patients) or 0.5 mg (paediatric and adolescent patients), and the maximum potential dose following the dose titration process was 3.0 mg or 2.5 mg daily depending on the maximum approved dose in the specific participating country as well as the age of the patient.

Number of subjects in period 1	All treated patients
Started	15
Completed	13
Not completed	2
Adverse event, serious fatal	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	All treated patients
Reporting group description:	
All patients treated with setmelanotide, includes a combination of 11 patients enrolled in a 'pivotal cohort' and 4 patients in a 'supplemental' cohort. All patients had the LEPR genetic mutation.	

Reporting group values	All treated patients	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	10	10	
Age continuous Units: years			
arithmetic mean	21.67		
standard deviation	± 8.52	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	6	6	
Body Mass Index Units: kg/m2			
arithmetic mean	49.21		
standard deviation	± 13.02	-	
Weight Units: kg			
arithmetic mean	132.46		
standard deviation	± 39.28	-	
Waist circumference Units: cm			
arithmetic mean	128.49		
standard deviation	± 24.15	-	

End points

End points reporting groups

Reporting group title	All treated patients

Reporting group description:

All patients treated with setmelanotide, includes a combination of 11 patients enrolled in a 'pivotal cohort' and 4 patients in a 'supplemental' cohort. All patients had the LEPR genetic mutation.

Primary: Body weight change

End point title	Body weight change[1]

End point description:

The primary endpoint in this study was defined as the proportion of patients who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment with setmelanotide, compared to the proportion from historical data (at most, 5% responders in the null population). This endpoint analysis was performed solely on designated responders and therefore on the FAS population.

The proportion of patients who had at least 10% weight reduction at ~1 year vs baseline was analysed via the exact binomial test, at 1-sided 5% of significance level, against the null hypothesis that the proportion was less than or equal to 5% and the alternative hypothesis was that the proportion was greater than 5%. The 2-sided 90% CI of the proportion was calculated using the exact Clopper-Pearson method.

Results of the analysis: point estimate: 53.3% (90% CI 30.0, 75.63), p<0.0001, indicating the primary efficacy endpoint was met.

End point type	Primary

End point timeframe:

Baseline to 1 year

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: In this non-comparator study, statistical analysis was based upon comparison with historical data. Details are included with the endpoint description since it is not possible to otherwise enter the analyses without a comparator group.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects				
Subjects with at least 10% weight loss	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight

End point title	Percentage change in body weight

End point description:

Mean percentage of body weight change (kg) from baseline after 1 year of treatment with setmelanotide within the DUS population (defined as all patients who received any study drug, demonstrated ≥5 kg weight loss or 5% of body weight over 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period).

A linear mixed model repeated measures analysis of variance with a fixed term for time and baseline and a random effect for patients was used. An unstructured covariance matrix was used to model the expected different variances among the participants. In the event the mixed model did not converge with an unstructured covariance matrix, a compound-symmetric then Toeplitz covariance matrix was employed instead.
Results of the analysis: LS mean change: -12.37 (90% CI -15.08, -9.66), p<0.0001, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

Change from baseline to Week 52

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: kg				
arithmetic mean (standard deviation)	-12.34 (± 7.534)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score

End point title	Change in hunger score

End point description:

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

A linear mixed model repeated measures analysis of variance with a fixed term for time and baseline and a random effect for patients was used. An unstructured covariance matrix was used to model the expected different variances among the participants. In the event the mixed model did not converge with an unstructured covariance matrix, a compound-symmetric then Toeplitz covariance matrix was employed instead.

Results of analysis: LS mean change: -42.69% (90% CI -56.35, -29.02), p<0.0001, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

From baseline to Week 52

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percent				
arithmetic mean (standard deviation)	-42.7 (± 27.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in daily hunger score

End point title	Improvement in daily hunger score

End point description:

Evaluation of the proportion of patients ≥12 years of age achieving at least 25% improvement in worst (most) hunger score following 1 year of treatment with setmelanotide. This endpoint analysis was performed solely on designated responders and therefore based on the FAS population.

The proportion of patients who had at least 25% improvement in hunger score at ~1 year vs baseline was analysed via the exact binomial test, at 1-sided 5% of significance level, against the null hypothesis that the proportion was less than or equal to 5% and the alternative hypothesis was that the proportion was greater than 5%. The 2-sided 90% CI of the proportion was calculated using the exact Clopper-Pearson method.

Results of the analysis: point estimate: 71.4% (90% CI 46.00, 89.60); p<0.0001, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

From baseline to Week 52.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Subjects with at least 25% improvement	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to end of treatment	
Adverse event reporting additional description:	
The relatedness assessment was as reported by the investigator.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	All treated patients
Reporting group description:	
All patients treated with setmelanotide, includes combination of 11 patients enrolled in a 'pivotal cohort' and 4 patients in a 'supplemental' cohort. All patients had the LEPR genetic mutation.	

Serious adverse events	All treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Gastric banding reversal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Suicidal ideation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Eye naevus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	32		
Injection site induration			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	16		
Injection site pain			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	14		
Injection site oedema			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	13		
Injection site pruritus			

subjects affected / exposed	8 / 15 (53.33%)			
occurrences (all)	13			
Fatigue				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	9			
Injection site bruising				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	8			
Asthenia				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences (all)	7			
Influenza like illness				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	4			
Injection site haematoma				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Injection site hypersensitivity				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Chest pain				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Malaise				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Injection site atrophy				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site reaction				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site urticaria				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Medical device pain				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Medical device site erythema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Xerosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	5		
Spontaneous penile erection			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Ejaculation disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Metrorrhagia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Amenorrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ovarian cyst			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vaginal haemorrhage			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Asthma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	7		
Anxiety			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Depressed mood			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Suicidal ideation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Affect lability			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Drug abuse			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fear of injection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Illusion			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood creatine phosphokinase abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood follicle stimulating hormone increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood luteinising hormone increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood urea decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Heart rate increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insulin tolerance test abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Weight increased			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac flutter			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	18		
Dizziness			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Sleep paralysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Presyncope			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Sciatica			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Syncope			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Eosinophilia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Iron deficiency anaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Tinnitus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	13		
Diarrhoea			

subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Gingival discolouration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatocellular injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	20		
Erythema			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Hyperhidrosis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin striae			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Hair growth rate abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperkeratosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lentigo			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lipodystrophy acquired			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Melanocytic naevus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pigmentation disorder			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Proteinuria subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Renal colic subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Renal failure subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Hypogonadism subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 7		
Arthralgia subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 4		
Musculoskeletal pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Gastrointestinal infection			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

Arthritis viral				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site abscess				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Dyslipidaemia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Folate deficiency				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Glucose tolerance impaired				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gout				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Vitamin A deficiency				

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2018	Substantive revisions made in this amendment were as follows: • Inclusion Criterion #2 was revised to include patients ≥6 years of age, and provided dose titration instructions and other applicable revisions to accommodate this younger patient population. • Revised the primary endpoint to a proportion of patients who met ≥10% weight loss rather than mean percent change from baseline. • Confirmed that more than 10 patients may have been enrolled if additional eligible patients were identified. • Clarified that OGTT was not to be performed for patients with a diagnosis of Type 1 or Type 2 diabetes. • Clarified that the schedule for obtaining samples for anti-drug antibodies was to be at Day 15 and Day 29 after initiation of dosing rather than on Day 15 and Day 29 after establishing the therapeutic dose. • Addition of QOL questionnaires SF-10, PedsQL, and C-SSRS (age-specific for patients ≥6 years of age. • Added bone X-rays. • Added WISC-V neurocognitive assessment. • Added an appendix that summarized blood volumes required for study assessments. • Added nutritional counselling for paediatric patients. • Clarified that for patients weighing <100 kg at baseline, a 5% change in weight was required to continue with study treatment rather than a 5 kg change in weight for patients weighing >100 kg at baseline.
31 July 2018	Substantive revisions made in this amendment were as follows. • Clarified that all Screening blood analyses were to be collected between Day -28 and Day -14. • Provided details regarding the Safety Monitoring Board used to monitor safety throughout the study to align with the current SAP at the request of the US Food and Drug Administration (FDA). • Clarified bone assessment schedule by adding a footnote that confirmed that bone age assessment was only required at the early termination visit and not at the final visit, as requested by the German Ethics Committee.
26 November 2018	The purpose of the amendment was to allow patients that experienced an adverse event or abnormal laboratory value an opportunity to be rechallenged with vehicle control (placebo) or lower doses of setmelanotide to further assess relatedness to study drug. If the Investigator wanted to further assess relatedness to study drug, the patient could have been re-challenged after approval by the Sponsor. Prior to re-challenging any patient, the Sponsor and Investigator were to define a re-challenge plan with certain parameters, specific to a particular patient. The addendum provided guidance and instructions to be followed when rechallenging a patient and assessing the data obtained during the re-challenge.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3313729