Clinical trial results:
Title: Setmelanotide (RM-493) treatment trial in patients with rare genetic disorders of obesity

Trial design: This was a Phase 2, open-label, uncontrolled, non-randomised, study with an additional long-term safety extension. The study planned to enrol up to 30 male and female patients with rare genetic obesity caused by a genetic mutation that impacts the leptin-melanocortin pathway (i.e., POMC, LEPR, MC4R, PCSK1 mutations, including heterozygous and epigenetic genetic defects in POMC, heterozygous MC4R mutations and patients with Bardet-Biedl and Alstrom's syndrome). The protocol was amended so that patients aged 12 years with a POMC mutation, LEPR mutation, MC4R variant mutation, or epigenetic variant mutation were eligible for study participation after efficacy had been established in adult patients.
After enrolment, patients entered a dose-finding phase (2-4 weeks), followed by an observation phase (4-11 weeks), during which they were treated with the optimal dose of setmelanotide as identified during dose-finding. After completion of this 12-week therapeutic dose level phase, patients were eligible to participate in a 2- to 4-week open-label drug-withdrawal phase, prior to continuation into a 2-year extension phase. During this extension phase, treatment with setmelanotide continued at the therapeutic dose level determined during the previous 12-week treatment period. The median duration of treatment was 405 days (range: 88 to 2060 days).
A small number of patients entered into the Rhythm long-term extension study RM-493-022 when study RM-493-011 was closed. They also continued longer term treatment with their therapeutic dose from the index study.

Summary

EudraCT number	2014-002392-28
Trial protocol	DE
Global end of trial date	17 December 2020
Results information	
Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	RM-493-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02507492
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité
Sponsor organisation address	Charité–Universitätsmedizin Berlin, Augustenburger Platz 1, 13353, Berlin, Germany,
Public contact	Institut für experimentelle pädiatrische Endokrinologie, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, 49 30450666839, peter.kuehnen@charite.de
Scientific contact	Institut für experimentelle pädiatrische Endokrinologie, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, 49 30450666839, peter.kuehnen@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2020
Global end of trial reached?	Yes
Global end of trial date	17 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess changes in body weight within four different populations of patients with rare genetic diseases of obesity following 3 months of setmelanotide treatment.

The patients had rare genetic diseases of obesity caused by genetic mutations that impacted the leptin melanocortin pathway (i.e., POMC, LEPR, MC4R, PCSK1 mutations, including heterozygous and epigenetic genetic defects in POMC, heterozygous MC4R mutations and patients with Bardet-Biedl

syndrome [BBS] and Alstrom’s syndrome [AS]).

Protection of trial subjects:

This trial was conducted in accordance with the current International Council on Harmonization (ICH) for Good Clinical Practice (GCP) guidelines. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Background therapy:

Additional concomitant medications were allowed with the express permission of the study investigators, but generally, efforts were made to only include medications considered medically necessary.

Due to the molecular nature of POMC mutations, which result in a lack of adrenocorticotropic hormone and mild hypothyroidism, POMC-deficient patients typically receive supplemental therapy with an oral hydrocortisone and in some instances L-thyroxine; therefore, these medications were allowed during the study.

Evidence for comparator:

Not applicable; all patients were treated with setmelanotide.

Actual start date of recruitment	11 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	13
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)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited 13 patients with rare genetic diseases of obesity in one centre in Germany from Dec 2014 to Sep 2020 (2 patients with POMC deficiency obesity, 3 patients with LEPR deficiency obesity, 5 patients with epigenetic mutations, and 3 patients with MC4R mutations).

Pre-assignment

Screening details:

Screening assessments included medical history, physical exam, diagnostic tests (gonadotropin-releasing hormone [GnRH] test, oral glucose tolerance test [OGTT], with insulin levels), laboratory tests, blood pressure, psychologist evaluation (including BDI2), hunger scale, body composition, and energy expenditure evaluation.

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	13

Period 1

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

Blinding implementation details:

Not applicable; this was an open-label study.

Arms

Are arms mutually exclusive?	No
Arm title	POMC

Arm description:

Patients with POMC deficiency obesity

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:

Setmelanotide was administered as a once daily subcutaneous (SC) injection at an initial dose of 0.5 mg, with monitoring for 12 h. Patients were re-admitted after 1 - 2 weeks and dose increases were based on assessments of body weight loss, hunger score, and assessment of AEs. The first POMC patient enrolled was dosed at 0.25 mg for the first week prior to titrating up to the 0.5 mg dose.

Setmelanotide dose was increased step-wise each week, as needed, as follows:
- Starting dose: 0.5 mg
- Step 2: 1 mg (1 week)
- Step 3: 1.5 mg (1 week)
- Step 4: 2 mg (1 week)

In adult patients, additional dose levels were permitted:
- Step 5: 2.5 mg (1 week)
- Step 6: 3.0 mg (1 week)

Increased dose levels were initially administered in the outpatient clinic. Once a patients' therapeutic

dose level was determined, this was continued by the patient for the remainder of the study. Dose determination expected to take 2 - 4 weeks. Treatment duration at established dose was 6 - 8 weeks.

Arm title	LEPR

Arm description:

Patients with LEPR deficiency obesity

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:

Setmelanotide was administered as a once daily (SC) injection at an initial dose of 0.5 mg, with monitoring for 12 h. Patients were re-admitted after 1 to 2 weeks and dose increases were based on assessments of body weight loss, hunger score, and assessment of AEs.

Setmelanotide dose was increased step-wise each week, as needed, as follows:
- Starting dose: 0.5 mg
- Step 2: 1 mg (for 1 week)
- Step 3: 1.5 mg (for 1 week)
- Step 4: 2 mg (for 1 week)

In adult patients, additional dose levels were permitted:
- Step 5: 2.5 mg (for 1 week)
- Step 6: 3.0 mg (for 1 week)

Each increased dose level was initially administered while patients were in the outpatient clinic. Once a patient’s therapeutic dose level was determined, the patient was to continue administration at that dose level for the remainder of the study. Dose determination was expected to take 2 to 4 weeks. Treatment duration at the established dose was 6 to 8 weeks.

Arm title	Epigenetic

Arm description:

Patients with epigenetic mutations related obesity

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:

Setmelanotide was administered as a once daily (SC) injection at an initial dose of 0.5 mg, with monitoring for 12 h. Patients were re-admitted after 1 to 2 weeks and dose increases were based on assessments of body weight loss, hunger score, and assessment of AEs.

Setmelanotide dose was increased step-wise each week, as needed, as follows:
- Starting dose: 0.5 mg
- Step 2: 1 mg (for 1 week)
- Step 3: 1.5 mg (for 1 week)
- Step 4: 2 mg (for 1 week)

In adult patients, additional dose levels were permitted:
- Step 5: 2.5 mg (for 1 week)
- Step 6: 3.0 mg (for 1 week)

Each increased dose level was initially administered while patients were in the outpatient clinic. Once a patient’s therapeutic dose level was determined, the patient was to continue administration at

that dose level for the remainder of the study. Dose determination was expected to take 2 to 4 weeks. Treatment duration at the established dose was 6 to 8 weeks.

Arm title	MC4R

Arm description:

Patients with MC4R mutations related obesity

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:

Setmelanotide was administered as a once daily (SC) injection at an initial dose of 0.5 mg, with monitoring for 12 h. Patients were re-admitted after 1 to 2 weeks and dose increases were based on assessments of body weight loss, hunger score, and assessment of AEs.

Setmelanotide dose was increased step-wise each week, as needed, as follows:
- Starting dose: 0.5 mg
- Step 2: 1 mg (for 1 week)
- Step 3: 1.5 mg (for 1 week)
- Step 4: 2 mg (for 1 week)

In adult patients, additional dose levels were permitted:
- Step 5: 2.5 mg (for 1 week)
- Step 6: 3.0 mg (for 1 week)

Each increased dose level was initially administered while patients were in the outpatient clinic. Once a patient’s therapeutic dose level was determined, the patient was to continue administration at that dose level for the remainder of the study. Dose determination was expected to take 2 to 4 weeks. Treatment duration at the established dose was 6 to 8 weeks.

Arm title	All patients

Arm description:

All patients with rare genetic diseases of obesity enrolled in this study.

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:

Setmelanotide was administered as a once daily (SC) injection at the doses as described above for each cohort in this study.

Number of subjects in period 1	POMC	LEPR	Epigenetic
Started	2	3	5
Completed	2	1	2
Not completed	0	2	3
Consent withdrawn by subject	-	-	1
Insufficient decrease of body weight	-	-	1
Lack of compliance	-	1	-
Not present at the visit despite reminders	-	1	1

Number of subjects in period 1	MC4R	All patients
Started	3	13
Completed	3	8
Not completed	0	5
Consent withdrawn by subject	-	1
Insufficient decrease of body weight	-	1
Lack of compliance	-	1
Not present at the visit despite reminders	-	2

Baseline characteristics

Reporting groups	
Reporting group title	POMC
Reporting group description: Patients with POMC deficiency obesity	
Reporting group title	LEPR
Reporting group description: Patients with LEPR deficiency obesity	
Reporting group title	Epigenetic
Reporting group description: Patients with epigenetic mutations related obesity	
Reporting group title	MC4R
Reporting group description: Patients with MC4R mutations related obesity	
Reporting group title	All patients
Reporting group description: All patients with rare genetic diseases of obesity enrolled in this study.	

Reporting group values	POMC	LEPR	Epigenetic
Number of subjects	2	3	5
Age categorical			
The age of patients at enrolment.			
Units: Subjects			
Adolescents (12-17 years)	0	1	0
Adults (18-64 years)	2	2	5
Gender categorical Units: Subjects			
Female	2	1	4
Male	0	2	1
Weight (kg) Units: kg			
median	153.9	122.1	137.6
full range (min-max)	152.8 to 155.0	120.6 to 130.6	89.8 to 182.2
BMI Units: kg/m2			
median	51.8	40.7	38.3
full range (min-max)	49.5 to 54.1	39.9 to 44.2	36.1 to 55.3
Hip Circumference (cm) Units: cm			
median	131.0	118.0	128.0
full range (min-max)	116.0 to 146.0	113.0 to 120.0	111.0 to 167.0
Waist Circumference (cm) Units: cm			
median	128.0	115.0	132.5
full range (min-max)	125.0 to 131.0	108.0 to 133.0	94.0 to 161.0

Reporting group values	MC4R	All patients	Total

Number of subjects	3	13	13
Age categorical			
The age of patients at enrolment.			
Units: Subjects			
Adolescents (12-17 years)	2	3	3
Adults (18-64 years)	1	10	10
Gender categorical Units: Subjects			
Female	2	9	9
Male	1	4	4
Weight (kg) Units: kg			
median	115.4	130.6	
full range (min-max)	102.2 to 148.2	89.8 to 182.2	-
BMI Units: kg/m2			
median	44.2	44.2	
full range (min-max)	41.2 to 46.5	36.1 to 55.3	-
Hip Circumference (cm) Units: cm			
median	123.0	120.0	
full range (min-max)	119.5 to 144.0	111.0 to 167.0	-
Waist Circumference (cm) Units: cm			
median	131.0	131.0	
full range (min-max)	116.0 to 151.0	94.0 to 161.0	-

End points

End points reporting groups

Reporting group title	POMC
Reporting group description:	
Patients with POMC deficiency obesity	
Reporting group title	LEPR
Reporting group description:	
Patients with LEPR deficiency obesity	
Reporting group title	Epigenetic
Reporting group description:	
Patients with epigenetic mutations related obesity	
Reporting group title	MC4R
Reporting group description:	
Patients with MC4R mutations related obesity	
Reporting group title	All patients
Reporting group description:	
All patients with rare genetic diseases of obesity enrolled in this study.	

Primary: Change in body weight - 3 months

End point title	Change in body weight - 3 months[1][2]
End point description:	
Change in body weight from baseline in each patient population after 3 months of setmelanotide treatment.	
End point type	Primary
End point timeframe:	
From baseline to 3 months.	

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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.
[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: All patients were treated with the same setmelanotide dose regimen. The numbers of patients ranged from 2 to 5 by indication (total = 13 patients). The total population (All patients) was primarily included for the evaluation of adverse events rather than efficacy, but in some cases was used in secondary endpoint analyses (in particular if few patients had data available for a particular endpoint, or if differences across cohorts were not of clinical interest).

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: kilogram(s)				
median (full range (min-max))	-23.15 (-25.8 to -20.5)	-10.00 (-17.5 to -5.4)	-7.60 (-9.4 to -2.5)	-6.10 (-6.5 to -4.5)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage change in body weight - 3 months

End point title	Percentage change in body weight - 3 months[3][4]

End point description:

Percentage change in body weight from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Primary

End point timeframe:

From baseline to 3 months.

Notes:

[3] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

[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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: percent				
median (full range (min-max))	-15.0 (-16.6 to -13.4)	-8.3 (-13.4 to -4.4)	-5.2 (-6.6 to -2.7)	-4.4 (-5.3 to -4.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight - 12 months

End point title	Change in body weight - 12 months[5]

End point description:

Change in body weight from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	2	1
Units: kilogram(s)				
median (full range (min-max))	-45.85 (-51.1 to -40.6)	-10.30 (-29.0 to 1.4)	-14.60 (-19.7 to -9.5)	-11.80 (-11.8 to -11.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight - 12 months

End point title	Percentage change in body weight - 12 months[6]

End point description:

Percentage change in body weight from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months

Notes:

[6] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	2	1
Units: percent				
median (full range (min-max))	-29.8 (-33.0 to -26.6)	-8.4 (-22.2 to 1.2)	-9.3 (-10.8 to -7.8)	-10.2 (-10.2 to -10.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight - 24 months

End point title	Change in body weight - 24 months[7]

End point description:

Median change in body weight from baseline in the overall patient population after 24 months of setmelanotide treatment (i.e., all patients with data at 24 months, regardless of underlying cause).

End point type	Secondary

End point timeframe:

From baseline to 24 months.

Notes:

[7] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: kilogram(s)				
median (full range (min-max))	-22.7 (-65.6 to -10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight - 24 months

End point title	Percentage change in body weight - 24 months[8]

End point description:

Percentage change in body weight from baseline in each patient population after 24 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 24 months.

Notes:

[8] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percent				
median (full range (min-max))	-15.7 (-42.3 to -8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in resting energy - 3 months

End point title	Change in resting energy - 3 months[9]

End point description:

Change in resting energy from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[9] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: kcal/day				
median (full range (min-max))	-288.0 (-309.0 to -267.0)	3.0 (-151.0 to 344.0)	98.0 (-77.0 to 601.0)	-294.0 (-394.0 to 164.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in resting energy - 12 months

End point title	Change in resting energy - 12 months[10]

End point description:

Change in resting energy from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[10] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: kcal/day				
median (full range (min-max))	-521.5 (-871.0 to -172.0)	-315.0 (-352.0 to -84.0)	194.0 (124.0 to 200.0)	-72.0 (-180.0 to -70.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in lean body mass - 3 months

End point title	Change in lean body mass - 3 months[11]

End point description:

Change in lean body mass from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months

Notes:

[11] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: kilogram(s)				
median (full range (min-max))	-3.25 (-3.9 to -2.6)	-2.70 (-5.0 to 3.2)	-2.90 (-54.1 to -0.4)	-3.60 (-6.3 to 50.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in lean body mass - 3 months

End point title	Percentage change in lean body mass - 3 months[12]

End point description:

Percentage change in lean body mass from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months

Notes:

[12] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: percent				
median (full range (min-max))	-5.020 (-5.68 to -4.36)	-3.808 (-7.58 to 4.34)	-4.489 (-45.93 to -0.88)	-7.362 (-8.45 to 461.47)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in lean body mass - 12 months

End point title	Change in lean body mass - 12 months[13]

End point description:

Change in lean body mass from baseline in each patient population after 12 months of setmelanotide

treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[13] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: kilogram(s)				
median (full range (min-max))	-5.95 (-11.2 to -0.7)	-7.40 (-10.4 to -4.6)	-5.70 (-22.4 to -0.1)	-2.10 (-7.4 to 48.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in lean body mass - 12 months

End point title	Percentage change in lean body mass - 12 months[14]

End point description:

Percentage change in lean body mass from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[14] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: percent				
median (full range (min-max))	-8.739 (-16.30 to -1.17)	-11.212 (-14.11 to -6.49)	-7.776 (-19.02 to -0.15)	-4.294 (-9.92 to 445.87)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fat mass - 3 months

End point title	Change in fat mass - 3 months[15]

End point description:

Change in fat mass from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[15] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: kilogram(s)				
median (full range (min-max))	-20.20 (-22.5 to -17.9)	-4.20 (-19.8 to -1.9)	-4.00 (-6.1 to 44.7)	-1.40 (-6.7 to 1.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in fat mass - 3 months

End point title	Percentage change in fat mass - 3 months[16]

End point description:

Percentage change in fat mass from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[16] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	5	3
Units: percent				
median (full range (min-max))	-22.639 (-26.07 to -19.21)	-7.692 (-35.17 to -3.79)	-7.143 (-7.64 to 69.20)	-2.647 (-12.36 to 2.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fat mass - 12 months

End point title	Change in fat mass - 12 months[17]

End point description:

Change in fat mass from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[17] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: kilogram(s)				
median (full range (min-max))	-36.30 (-39.0 to -33.6)	-6.00 (-15.8 to -0.8)	-0.80 (-9.2 to 6.2)	-5.40 (-46.5 to -2.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in fat mass - 12 months

End point title	Percentage change in fat mass - 12 months[18]

End point description:

Percentage change in fat mass from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[18] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: percent				
median (full range (min-max))	-40.621 (-45.19 to -36.05)	-11.976 (-28.06 to -1.47)	-1.274 (-16.43 to 9.60)	-9.963 (-64.23 to -4.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score - 3 months

End point title	Change in hunger score - 3 months[19]

End point description:

Change in hunger score from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[19] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	3
Units: 10-point scale				
median (full range (min-max))	-8.5 (-9 to -8)	-7.0 (-7 to -4)	-3.0 (-4 to -1)	-6.0 (-6 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in hunger score - 3 months

End point title	Percentage change in hunger score - 3 months[20]

End point description:

Percentage change in hunger score from baseline in each patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[20] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	3
Units: percent				
median (full range (min-max))	-89.4 (-90 to -89)	-70.0 (-78 to -44)	-47.3 (-60 to -17)	-75.0 (-86 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score - 12 months

End point title	Change in hunger score - 12 months[21]

End point description:

Change in hunger score from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[21] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: 10-point scale				
median (full range (min-max))	-7.0 (-8 to -6)	-5.0 (-7 to -4)	-1.0 (-2 to -1)	1.0 (-4 to 2)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in hunger score - 12 months

End point title	Percentage change in hunger score - 12 months[22]

End point description:

Percentage change in hunger score from baseline in each patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[22] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	POMC	LEPR	Epigenetic	MC4R
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	3
Units: percent				
median (full range (min-max))	-73.3 (-80 to -67)	-55.6 (-78 to -40)	-16.7 (-29 to -13)	25.0 (-57 to 33)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HOMA-IR - 3 months

End point title	Change in HOMA-IR - 3 months[23]

End point description:

Change in HOMA-IR index from baseline in the total patient population after 3 months of setmelanotide treatment. HOMA-IR is calculated using the following formula:
(HOMA-IR = [glucose] (mmol/L) × [insulin] (μU/mL)/22.5).

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[23] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: HOMA-IR Index				
median (full range (min-max))	-0.020 (-0.13 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HOMA-IR - 12 months

End point title	Change in HOMA-IR - 12 months[24]

End point description:

Change in HOMA-IR index from baseline in the total patient population after 12 months of setmelanotide

treatment. HOMA-IR is calculated using the following formula:
(HOMA-IR = [glucose] (mmol/L) × [insulin] (µU/mL)/22.5).

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[24] - 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: See primary endpoint above "Change in body weight - 3 months" for detailed justification.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: HOMA-IR Index				
median (full range (min-max))	-0.020 (-0.12 to -0.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting glucose - 3 months

End point title	Change in fasting glucose - 3 months[25]

End point description:

Change in fasting glucose from baseline in the total patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[25] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mg/dL				
median (full range (min-max))	-24.0 (-68 to -2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting glucose - 12 months

End point title	Change in fasting glucose - 12 months[26]

End point description:

Change in fasting glucose from baseline in the total patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[26] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mg/dL				
median (full range (min-max))	-54.0 (-66 to 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting insulin - 3 months

End point title	Change in fasting insulin - 3 months[27]

End point description:

Change in fasting insulin from baseline in the total patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[27] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mU/L				
median (full range (min-max))	-92.500 (-372.14 to 2.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting insulin - 12 months

End point title	Change in fasting insulin - 12 months[28]

End point description:

Change in fasting insulin from baseline in the total patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[28] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mU/L				
median (full range (min-max))	-119.970 (-345.10 to -39.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HBA1c - 3 months

End point title	Change in HBA1c - 3 months[29]

End point description:

Change in HBA1c (%) from baseline in the total patient population after 3 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 3 months.

Notes:

[29] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13

patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent				
median (full range (min-max))	-0.10 (-0.3 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HBA1c - 12 months

End point title	Change in HBA1c - 12 months[30]

End point description:

Change in HBA1c (%) from baseline in the total patient population after 12 months of setmelanotide treatment.

End point type	Secondary

End point timeframe:

From baseline to 12 months.

Notes:

[30] - 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 2 to 5 by indication, with an overall total of 13 patients. Data were summarised using descriptive statistics only.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
median (full range (min-max))	-0.20 (-0.3 to 0.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported throughout the study. The median duration of treatment was 405 days (range: 88 to 2060 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Total

Reporting group description:

All patients treated with setmelanotide in this study.

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	7		
Injection site erythema			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Injection site reaction			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Injection site oedema			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Injection site pruritus			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		

Injection site discolouration subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Injection site haematoma subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Injection site induration subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Injection site nodule subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Injection site swelling subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 3		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3		
Depressed mood subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Mood altered subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

Restlessness subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Injury, poisoning and procedural complications Concussion subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all) Lower limb fracture subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	 7 / 13 (53.85%) 13 1 / 13 (7.69%) 8		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain	 6 / 13 (46.15%) 11 4 / 13 (30.77%) 4		

subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Frequent bowel movements subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation subjects affected / exposed occurrences (all)	10 / 13 (76.92%) 12		
Alopecia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Madarosis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	11		
Gastroenteritis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pharyngitis			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2014	Protocol Amendment 1 included the following revisions to the original protocol: • Treatment of younger patients with the POMC null genetic deficiency (12 years of age and older). • Adjustment of the initial dose level of setmelanotide and subsequent dose escalation procedure based on results of the first patient. • Revisions to study procedures to include pharmacokinetics (PK) measurement of setmelanotide at a scheduled study visit. • Addition of 24-hour ambulatory blood pressure monitoring (ABPM) to more closely evaluate potential changes in blood pressure and heart rate.
31 August 2015	Amendments 2 and 2.1 were not approved by the local CA. All elements of Amendments 2 and 2.1 were therefore included, submitted, and approved in Amendment 3. Protocol Amendment 3 provided the following revisions to the study protocol: •Increased the starting dose of setmelanotide from 0.25 mg to 0.5 mg in the dose titration phase of the study. •Decreased the interval of dose escalations from 2 weeks to 1 week. •Added procedures at the final visit examination after the third phase of the study to accommodate a planned pharmacodynamic analysis. Additional serum samples were intended to permit correlation analysis of setmelanotide PK. •Added a 24-hour blood pressure measurement on the day before the final visit examination. Also, the study was extended to a duration of 1-2 years. If a patient lost sufficient body weight during the first 12 weeks in the study without significant adverse events reported and agreed to provide consent to continue treatment with setmelanotide, they were eligible to participate in an extension phase. The following revisions were included in this amendment to accommodate this extension of setmelanotide treatment: •Extension of treatment duration for 1 year (ability to continue in 1-year increments; with careful monitoring of the vital signs; continuation for another year after confirmation by BfArM (up to a maximum of a total 2-year treatment period). •Regular visits at least every 3 months with the study doctor. •Full safety laboratory evaluations including OGTT, GnRH test every 6 months. •Consultation with a dermatologist every 6 months. •Daily measurements of blood pressure (once daily) at home, and additional blood pressure monitoring at study site visits. •A brief report summarizing the study course to be sent to the CA every 8 weeks.
18 October 2015	Protocol Amendment 4 included the following revisions to the original protocol: Based upon promising results demonstrating efficacy and safety in 2 adult POMC deficient patients participating in the study, the study inclusion criteria were revised to include adult LEPR and PCSK1 deficient patients.

22 January 2016	Protocol Amendment 5 included the following revisions to the original protocol: The study was amended to allow inclusion of non-adult, adolescent POMC patients 12 years of age and older. In addition, the amendment included the following additional monitoring steps. 1. During the first 3 months of treatment, non-adult patients were to be examined by a paediatrician once a week, and the investigator was to have weekly contact (phone call or clinic visit). 2. The patients were to be seen by the investigator every 4 weeks during the first 3 months. 3. Blood pressure measurements 3 times daily. 4. A brief progress report regarding chronic animal toxicology findings was to be provided by Rhythm Pharmaceuticals every 4 weeks. 5. Patients that entered the extension portion of the study were to be examined by the investigator every 3 months, and laboratory testing (liver function, complete blood count, and metabolic parameters) and dermatological examinations performed. Every 6 months laboratory testing was to include OGTT and GnRH testing.
05 September 2016	Protocol Amendment 6.1 included the following revisions. 1. Renamed protocol to clarify this protocol studied a broad range of rare monogenic causes of obesity related to the MC4 pathway. 2. Inclusion of the following obese patient populations with genetic mutations impacting the leptin-melanocortin pathway: • Heterozygous POMC mutations • POMC hypermethylation • Bardet-Biedl syndrome • Alstrom's Syndrome 3. Based on initial clinical data in an adult LEPR patient, this amendment included non-adult, adolescent LEPR patients (≥12 years of age). 4. Outlined specific entry procedures related to non-adult, adolescent patients (≥12 years of age). 5. Allowed a short period of treatment withdrawal for consenting patients who qualified for inclusion in the extension phase.
24 November 2016	Protocol Amendment 7 included the following revisions to the original protocol: This protocol amendment revised the maximum setmelanotide dose level administered to adult patients up to 2.5 mg and revised the weight loss criterion for entering the extension portion of the study from 8 kg to 5 kg of total weight reduction during the initial treatment phase of the study.
18 January 2018	Protocol Amendment 8 included the following revisions to the original protocol: This protocol amendment provided for the inclusion of MC4R variant carriers in the study and established a further extension of treatment with setmelanotide beyond 2 years (elongation portion). This amendment also revised the maximum setmelanotide dose level administered to adult patients up to 3.0 mg.
27 June 2019	Protocol Amendment 9 included the following revisions to the original protocol: This protocol amendment assigned a subinvestigator and established the previous investigator as the principal investigator. It also expanded eligibility to epigenetic variant non-adult patients (12 years of age and older) and implemented the use of a dosing diary.
21 November 2019	Protocol Amendment 10 included the following revisions to the original protocol: A change from single-use vials to multiple-use vials was incorporated into this amendment. Patients received written instructions in addition to injection training.
18 February 2020	Protocol Amendment 11 included the following revisions to the original protocol: This amendment provided the rationale for inclusion of non-adult MC4R deficient patients ≥12 years of age.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sample size was driven by clinical considerations. Due to the rarity of individuals with rare genetic diseases of obesity, it was anticipated that only up to 5 patients with each rare genetic disorder would potentially be recruited.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27468060

http://www.ncbi.nlm.nih.gov/pubmed/2973602