



Clinical trial results:

Title: Setmelanotide (RM-493) phase 2 treatment trial in patients with rare genetic disorders of obesity.

Trial design: This was a Phase 2, open-label, uncontrolled, non-randomised, proof-of-concept study over 20 weeks post-screening, with the possibility of enrolment in a separate extension study at Week 16 (study RM-493-022). It was planned to enrol approximately 235 obese patients with rare genetic diseases of obesity (RGDO) caused by genetic mutations that impact the leptin-melanocortin hypothalamic pathway (the MC4R pathway), including one of the following 10 cohorts, which shared the phenotype of early onset obesity and hyperphagia: chromosomal rearrangement of the 16p11.2 locus, Alström Syndrome (AS), Bardet Biedl Syndrome (BBS), MC4R deficiency, PPL (collective name for POMC, PCSK1, and LEPR deficiency) heterozygous, PPL composite heterozygous, PPL compound heterozygous, SH2B1 deficiency, Smith-Magenis Syndrome (SMS), and SRC1 deficiency. The protocol was amended so that patients 6 years and older with RGDO were eligible for participation. The study consisted of a 2-8 week screening period and a 16-week treatment period.

After enrolment, patients entered a screening period when they completed a daily hunger questionnaire. During the treatment period, all patients initiated treatment with setmelanotide and dose escalated to the final dose of 3.0 mg once daily (QD). Patients continued dosing at 3.0 mg QD and returned to the clinic every 4 weeks (at Visits 3-5) to complete all study assessments. After 16 weeks, at Visit 6, the patient received the last setmelanotide injection and participation in the study concluded in one of the following 2 ways:

- Completed Visit 6 and enrolled in a separate extension study, Rhythm Study RM-493-022.
- Decided not to participate in the extension study and proceeded to the final study visit (Visit 7) at Week 20.

The median duration of treatment was 17 weeks (range: 1 to 96 weeks).

Summary

EudraCT number	2017-000387-14
Trial protocol	GB ES DE FR NL GR
Global end of trial date	01 March 2022

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	RM-493-014
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03013543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rhythm Pharmaceuticals, Inc,
Sponsor organisation address	222 Berkeley Street, 12th Floor, Boston, United States, MA 02116
Public contact	Rhythm Clinical Trials, Rhythm Pharmaceuticals, Inc, +1 8572644280, clinicaltrials@rhythmtx.com
Scientific contact	Rhythm Clinical Trials, Rhythm Pharmaceuticals, Inc, +1 8572644280, clinicaltrials@rhythmtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	02 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2022
Global end of trial reached?	Yes
Global end of trial date	01 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to explore the impact of setmelanotide on obesity in patients with various specific RGDO.

Protection of trial subjects:

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) reviewed all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study was only conducted at sites where IRB/IEC approval had been obtained.

This study was conducted in accordance with:

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

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

Data Safety Monitoring (DSM) was the responsibility of the Investigator, on an ongoing basis, rather than an internal safety monitoring committee. The study was also monitored by a DSM Board with outside advisors who met periodically.

Background therapy:

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

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

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

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

Evidence for comparator:

Not applicable.

Actual start date of recruitment	10 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 119
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 23

Country: Number of subjects enrolled	Greece: 5
Worldwide total number of subjects	213
EEA total number of subjects	60

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)	27
Adolescents (12-17 years)	63
Adults (18-64 years)	118
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited 213 patients with RGDO in 57 centres in Europe, Israel, Canada, and the United States with the first patient enrolled on 10 Feb 2017 and the last patient visit on 01 Mar 2022. Patients were included if they had RDGO for which evidence supported a role of the leptin-melanocortin hypothalamic pathway (i.e., the MC4R pathway).

Pre-assignment

Screening details:

Screening assessments included medical history, physical exam, comprehensive skin examination, laboratory tests, blood pressure, hunger scale, body composition, Columbia-Suicide Severity Rating Scale (C-SSRS) form, and energy expenditure evaluation.

Period 1

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

Blinding implementation details:

This was an open-label, proof-of-concept study.

Arms

Are arms mutually exclusive?	No
Arm title	16.p11.2

Arm description:

Patients with RGDO caused by deletions in the p11.2 region of chromosome 16 encompassing the SH2B1 gene.

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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	AS - Alstrom Syndrome
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Arm description:

Patients with RGDO caused by Alström Syndrome (AS). AS is a ciliopathy characterised by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus.

Arm type	Experimental
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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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	BBS - BardetBiedl syndrome
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Arm description:

Patients with RGDO caused by BBS. BBS is a genetically heterogeneous human obesity syndrome associated with ciliary dysfunction.

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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	MC4R
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Arm description:

Patients with RGDO with heterozygous loss-of-function MC4R variants. MC4R variants were categorized into subgroups based upon whether setmelanotide could elicit MC4R receptor activation. Activation was measured based on relative cAMP signaling between setmelanotide and alpha-MSH.

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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg

QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	PPL Heterozygous
Arm description: Patients with RGDO carrying heterozygous loss of function variants in POMC, PCSK1, or LEPR, causing early onset hyperphagia and 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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	PPL Composite Heterozygous
Arm description: Patients with RGDO carrying 2 or more heterozygous loss of function mutations in 2 or more of POMC, PCSK1, or LEPR, causing early onset hyperphagia and 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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	PPL Compound Heterozygous
Arm description: Patients with RGDO carrying 2 different heterozygous loss of function mutations in POMC, PCSK1, or LEPR, causing early onset hyperphagia and 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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	SH2B1
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Arm description:

Patients with RGDO caused by SRC homology 2 B adapter protein 1 (SH2B1) loss-of-function mutations.

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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	SMS - Smith-Magenis Syndrome
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Arm description:

Patients with RGDO caused by SMS, a complex genetic disorder characterised by sleep disturbance, multiple developmental anomalies, psychiatric behaviour, and obesity. It is caused by a heterozygous 17p11.2 microdeletion containing the retinoic acid-induced 1 (RAI1) gene or mutation within RAI1. RAI1 haplo-insufficiency is thought to contribute to obesity through downregulation of brain-derived neurotrophic factor (BDNF) and POMC.

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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	SRC1
Arm description:	
Patients with RGDO caused by Steroid Receptor Coactivator-1 Deficiency (SRC1) gene deficiency.	
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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Arm title	Overall
Arm description:	
The overall total of patients with RGDO from each arm.	
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 once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. After protocol amendment 9, the standard dose escalation was: Patients <16 years of age: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16. Patients ≥16 years of age: 2.0 mg in Weeks 1-2, and 3.0 mg between Weeks 3-16.

Before amendment 9, dose titration was in 0.5 mg increments at 1-2 week intervals starting with 1.0 mg QD until a therapeutic dose was achieved or until the patient reached a maximum dose of 2.5 mg QD (prior to Amendment 6) or 3.0 mg QD (from Amendment 6). In the UK, the maximum doses were 2.0 mg and 2.5 mg, respectively, in adolescents and children.

Number of subjects in period 1	16.p11.2	AS - Alstrom Syndrome	BBS - BardetBiedl syndrome
Started	19	4	10
Completed	19	2	7
Not completed	0	2	3
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	2	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Other	-	-	2
Withdrawal by Parent/Guardian	-	-	1
Non-compliance with study drug	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	MC4R	PPL Heterozygous	PPL Composite Heterozygous
Started	49	33	5
Completed	37	22	2
Not completed	12	11	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	5	6	2
Physician decision	-	1	-
Adverse event, non-fatal	3	2	1
Other	-	2	-
Withdrawal by Parent/Guardian	1	-	-
Non-compliance with study drug	-	-	-
Lost to follow-up	1	-	-
Lack of efficacy	1	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	PPL Compound Heterozygous	SH2B1	SMS - Smith-Magenis Syndrome
Started	27	22	12
Completed	20	13	9
Not completed	7	9	3
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	3	1	-
Physician decision	-	-	-
Adverse event, non-fatal	3	8	-
Other	-	-	1
Withdrawal by Parent/Guardian	-	-	1

Non-compliance with study drug	-	-	1
Lost to follow-up	1	-	-
Lack of efficacy	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	SRC1	Overall
Started	32	213
Completed	22	153
Not completed	10	60
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	23
Physician decision	-	1
Adverse event, non-fatal	2	19
Other	-	5
Withdrawal by Parent/Guardian	1	4
Non-compliance with study drug	-	1
Lost to follow-up	2	4
Lack of efficacy	-	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	16.p11.2
Reporting group description: Patients with RGDO caused by deletions in the p11.2 region of chromosome 16 encompassing the SH2B1 gene.	
Reporting group title	AS - Alstrom Syndrome
Reporting group description: Patients with RGDO caused by Alström Syndrome (AS). AS is a ciliopathy characterised by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus.	
Reporting group title	BBS - BardetBiedl syndrome
Reporting group description: Patients with RGDO caused by BBS. BBS is a genetically heterogeneous human obesity syndrome associated with ciliary dysfunction.	
Reporting group title	MC4R
Reporting group description: Patients with RGDO with heterozygous loss-of-function MC4R variants. MC4R variants were categorized into subgroups based upon whether setmelanotide could elicit MC4R receptor activation. Activation was measured based on relative cAMP signaling between setmelanotide and alpha-MSH.	
Reporting group title	PPL Heterozygous
Reporting group description: Patients with RGDO carrying heterozygous loss of function variants in POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	PPL Composite Heterozygous
Reporting group description: Patients with RGDO carrying 2 or more heterozygous loss of function mutations in 2 or more of POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	PPL Compound Heterozygous
Reporting group description: Patients with RGDO carrying 2 different heterozygous loss of function mutations in POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	SH2B1
Reporting group description: Patients with RGDO caused by SRC homology 2 B adapter protein 1 (SH2B1) loss-of-function mutations.	
Reporting group title	SMS - Smith-Magenis Syndrome
Reporting group description: Patients with RGDO caused by SMS, a complex genetic disorder characterised by sleep disturbance, multiple developmental anomalies, psychiatric behaviour, and obesity. It is caused by a heterozygous 17p11.2 microdeletion containing the retinoic acid-induced 1 (RAI1) gene or mutation within RAI1. RAI1 haplo-insufficiency is thought to contribute to obesity through downregulation of brain-derived neurotrophic factor (BDNF) and POMC.	
Reporting group title	SRC1
Reporting group description: Patients with RGDO caused by Steroid Receptor Coactivator-1 Deficiency (SRC1) gene deficiency.	
Reporting group title	Overall
Reporting group description: The overall total of patients with RGDO from each arm.	

Reporting group values	16.p11.2	AS - Alstrom Syndrome	BBS - BardetBiedl syndrome
Number of subjects	19	4	10
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	21.4 ± 14.58	16.0 ± 3.74	22.5 ± 14.71
Gender categorical Units: Subjects			
Female	13	3	6
Male	6	1	4
Weight at baseline			
Patient weight at baseline.			
Units: kilogram(s) arithmetic mean standard deviation	113.62 ± 38.489	87.28 ± 16.360	128.04 ± 28.631
Waist Circumference at Baseline			
Patient waist circumference at baseline.			
Units: centimetre arithmetic mean standard deviation	116.84 ± 22.179	109.75 ± 14.523	126.20 ± 19.344
BMI at Baseline			
Patient BMI at baseline.			
Body Mass Index: calculated as weight (kg) / height (m2).			
Units: kilogram(s)/square metre arithmetic mean standard deviation	41.68 ± 10.697	35.62 ± 8.445	44.83 ± 4.068

Reporting group values	MC4R	PPL Heterozygous	PPL Composite Heterozygous
Number of subjects	49	33	5
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	22.4 ± 15.28	36.1 ± 17.23	40.4 ± 19.62
Gender categorical Units: Subjects			
Female	27	22	4
Male	22	11	1
Weight at baseline			
Patient weight at baseline.			
Units: kilogram(s) arithmetic mean standard deviation	117.87 ± 32.339	143.04 ± 30.492	139.05 ± 30.957
Waist Circumference at Baseline			
Patient waist circumference at baseline.			

Units: centimetre			
arithmetic mean	122.52	137.95	134.00
standard deviation	± 19.697	± 18.529	± 19.038
BMI at Baseline			
Patient BMI at baseline.			
Body Mass Index: calculated as weight (kg) / height (m2).			
Units: kilogram(s)/square metre			
arithmetic mean	42.49	50.78	50.89
standard deviation	± 8.346	± 11.301	± 5.674

Reporting group values	PPL Compound Heterozygous	SH2B1	SMS - Smith-Magenis Syndrome
Number of subjects	27	22	12
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	30.7	33.6	19.4
standard deviation	± 20.16	± 17.88	± 8.10
Gender categorical			
Units: Subjects			
Female	18	15	10
Male	9	7	2
Weight at baseline			
Patient weight at baseline.			
Units: kilogram(s)			
arithmetic mean	122.08	129.06	92.48
standard deviation	± 43.315	± 39.480	± 24.556
Waist Circumference at Baseline			
Patient waist circumference at baseline.			
Units: centimetre			
arithmetic mean	128.52	130.28	110.14
standard deviation	± 28.772	± 23.029	± 11.807
BMI at Baseline			
Patient BMI at baseline.			
Body Mass Index: calculated as weight (kg) / height (m2).			
Units: kilogram(s)/square metre			
arithmetic mean	46.06	48.18	38.85
standard deviation	± 13.255	± 13.487	± 8.656

Reporting group values	SRC1	Overall	Total
Number of subjects	32	213	213
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	31.3	28.1	
standard deviation	± 17.13	± 17.30	-

Gender categorical			
Units: Subjects			
Female	25	143	143
Male	7	70	70
Weight at baseline			
Patient weight at baseline.			
Units: kilogram(s)			
arithmetic mean	124.07	122.98	
standard deviation	± 33.717	± 36.142	-
Waist Circumference at Baseline			
Patient waist circumference at baseline.			
Units: centimetre			
arithmetic mean	123.10	125.63	
standard deviation	± 21.101	± 22.162	-
BMI at Baseline			
Patient BMI at baseline.			
Body Mass Index: calculated as weight (kg) / height (m2).			
Units: kilogram(s)/square metre			
arithmetic mean	45.79	45.21	
standard deviation	± 11.097	± 11.048	-

End points

End points reporting groups

Reporting group title	16.p11.2
Reporting group description: Patients with RGDO caused by deletions in the p11.2 region of chromosome 16 encompassing the SH2B1 gene.	
Reporting group title	AS - Alstrom Syndrome
Reporting group description: Patients with RGDO caused by Alström Syndrome (AS). AS is a ciliopathy characterised by a syndromic phenotype that includes progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, congestive heart failure, and marked childhood obesity associated with hyperinsulinemia and type 2 diabetes mellitus.	
Reporting group title	BBS - BardetBiedl syndrome
Reporting group description: Patients with RGDO caused by BBS. BBS is a genetically heterogeneous human obesity syndrome associated with ciliary dysfunction.	
Reporting group title	MC4R
Reporting group description: Patients with RGDO with heterozygous loss-of-function MC4R variants. MC4R variants were categorized into subgroups based upon whether setmelanotide could elicit MC4R receptor activation. Activation was measured based on relative cAMP signaling between setmelanotide and alpha-MSH.	
Reporting group title	PPL Heterozygous
Reporting group description: Patients with RGDO carrying heterozygous loss of function variants in POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	PPL Composite Heterozygous
Reporting group description: Patients with RGDO carrying 2 or more heterozygous loss of function mutations in 2 or more of POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	PPL Compound Heterozygous
Reporting group description: Patients with RGDO carrying 2 different heterozygous loss of function mutations in POMC, PCSK1, or LEPR, causing early onset hyperphagia and obesity.	
Reporting group title	SH2B1
Reporting group description: Patients with RGDO caused by SRC homology 2 B adapter protein 1 (SH2B1) loss-of-function mutations.	
Reporting group title	SMS - Smith-Magenis Syndrome
Reporting group description: Patients with RGDO caused by SMS, a complex genetic disorder characterised by sleep disturbance, multiple developmental anomalies, psychiatric behaviour, and obesity. It is caused by a heterozygous 17p11.2 microdeletion containing the retinoic acid-induced 1 (RAI1) gene or mutation within RAI1. RAI1 haplo-insufficiency is thought to contribute to obesity through downregulation of brain-derived neurotrophic factor (BDNF) and POMC.	
Reporting group title	SRC1
Reporting group description: Patients with RGDO caused by Steroid Receptor Coactivator-1 Deficiency (SRC1) gene deficiency.	
Reporting group title	Overall
Reporting group description: The overall total of patients with RGDO from each arm.	

Primary: Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline

End point title	Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline ^{[1][2]}
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End point description:

The proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~3 months of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

End point type	Primary
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End point timeframe:

From baseline to after 3 months of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 1 to 34 by RGDO mutation, with an overall total of 213 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. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percent				
number (confidence interval 90%)	30.5 (25.3 to 36.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - <12 years

End point title	Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - <12 years ^[3]
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End point description:

The proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~3 months of treatment with setmelanotide by age categories (<12 years). The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

End point type	Secondary
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End point timeframe:

From baseline to 3 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percent				
number (confidence interval 90%)				
<12 years old	11.1 (3.1 to 26.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 12 and < 18 years

End point title	Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 12 and < 18 years ^[4]
End point description: The proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~3 months of treatment with setmelanotide by age categories (≥ 12 and < 18 years). The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.	
End point type	Secondary
End point timeframe: From baseline to 3 months	

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: percent				
number (confidence interval 90%)				
≥ 12 and < 18 years	31.7 (22.1 to 42.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 18 years

End point title	Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 18 years ^[5]
End point description: The proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~3 months of treatment with setmelanotide by age	

categories (≥ 18 years). The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

End point type	Secondary
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End point timeframe:

From baseline to 3 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: percent				
number (confidence interval 90%)				
≥ 18 years	34.1 (27.1 to 41.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 12 Years

End point title	Percentage of Patients who achieved $\geq 5\%$ Reduction in Body Weight from Baseline - ≥ 12 Years ^[6]
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End point description:

The proportion of patients in each subgroup of RGDO who achieve at least 5% reduction from baseline in body weight (i.e., are 'responders') after ~ 3 months of treatment with setmelanotide by age categories (≥ 12 Years). The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

End point type	Secondary
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End point timeframe:

From baseline to 3 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 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	186			
Units: percent				
number (confidence interval 90%)				
≥ 12 Years	33.3 (27.6 to 39.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Body Weight change from Baseline to 3 months

End point title	Percentage Body Weight change from Baseline to 3 months ^[7]
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End point description:

End point type	Secondary
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End point timeframe:

From baseline to 3 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percent				
arithmetic mean (standard deviation)	-2.74 (± 4.746)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in Weekly Average of Daily Most Hunger Score from Baseline to 3 months

End point title	Percentage change in Weekly Average of Daily Most Hunger Score from Baseline to 3 months ^[8]
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End point description:

End point type	Secondary
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End point timeframe:

From baseline to 3 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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: percent				
arithmetic mean (standard deviation)	-37.70 (\pm 36.762)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in Waist Circumference from Baseline to 3 months

End point title	Percentage change in Waist Circumference from Baseline to 3 months ^[9]
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End point description:

End point type	Secondary
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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: All patients were treated with the same setmelanotide dose regimen. There was no comparators group. The numbers of patients ranged from 4 to 49 by RGDO mutation, with an overall total of 213 patients. Data were summarised using descriptive statistics only.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: percent				
arithmetic mean (standard deviation)	-2.35 (\pm 8.420)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to 3 months.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Overall
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Reporting group description:

All patients treated with setmelanotide during the study.

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 213 (3.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 213 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Typical aura without headache			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotavirus infection			
subjects affected / exposed	1 / 213 (0.47%)		
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	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	208 / 213 (97.65%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	50 / 213 (23.47%)		
occurrences (all)	61		
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 213 (28.17%)		
occurrences (all)	90		
Dizziness			
subjects affected / exposed	15 / 213 (7.04%)		
occurrences (all)	16		
General disorders and administration site conditions			

Injection site pruritus subjects affected / exposed occurrences (all)	35 / 213 (16.43%) 45		
Injection site erythema subjects affected / exposed occurrences (all)	29 / 213 (13.62%) 39		
Fatigue subjects affected / exposed occurrences (all)	34 / 213 (15.96%) 38		
Injection site induration subjects affected / exposed occurrences (all)	14 / 213 (6.57%) 18		
Injection site pain subjects affected / exposed occurrences (all)	13 / 213 (6.10%) 16		
Injection site oedema subjects affected / exposed occurrences (all)	11 / 213 (5.16%) 14		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all)	12 / 213 (5.63%) 14		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	82 / 213 (38.50%) 110		
Vomiting subjects affected / exposed occurrences (all)	32 / 213 (15.02%) 41		
Diarrhoea subjects affected / exposed occurrences (all)	23 / 213 (10.80%) 23		
Abdominal pain upper subjects affected / exposed occurrences (all)	16 / 213 (7.51%) 18		
Abdominal pain			

subjects affected / exposed occurrences (all)	12 / 213 (5.63%) 12		
Reproductive system and breast disorders Erection increased subjects affected / exposed occurrences (all)	20 / 213 (9.39%) 23		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 213 (5.16%) 12		
Skin and subcutaneous tissue disorders Skin hyperpigmentation subjects affected / exposed occurrences (all) Macule subjects affected / exposed occurrences (all)	160 / 213 (75.12%) 351 12 / 213 (5.63%) 67		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	13 / 213 (6.10%) 13		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	18 / 213 (8.45%) 19		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 213 (5.16%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2017	<p>Amendment 1.0</p> <ul style="list-style-type: none">• 2 Global Hunger Questions were added to the study to help assess hunger.• Coagulation assessments (coagulation profile (prothrombin time [PT] or international normalised ratio [INR], and partial thromboplastin time [PTT], also referred to as activated partial thromboplastin time [aPTT])) were added to safety laboratories.• For patient safety, it was clarified that the oral glucose tolerance test would not be done on patients with a diagnosis of Type 1 or Type 2 diabetes.• The list of specific hormonal, neuroendocrine, metabolic, and anti-inflammatory analytes and biomarkers to be analysed was removed from the exploratory objective.
21 March 2018	<p>Amendment 6.0</p> <ul style="list-style-type: none">• The dose titration schedule was clarified to allow for a possible second dose titration during the dose titration phase or the 10-week open label phase, if deemed necessary by the Investigator after consultation with the Sponsor.• The dose titration table was updated to clarify the maximum dose for adults and adolescents and the maximum dose for both in all countries.• Clarified that the definition of non-child bearing potential was the start of menarche and is not a criterion for Tanner Staging• The possibility of conducting certain visits at a patient's local physician's office was removed due to administrative and regulatory constraints. Home nursing visits arranged by Sponsor will still be possible for these visits.• Females who were breastfeeding or nursing were excluded globally• Added a statement regarding contraception required by UK regulatory authorities for females who reached Tanner Stage 5 or achieved menarche during the study and added a statement required by UK regulatory authorities regarding true abstinence.
28 June 2018	<p>Amendment 7.0</p> <ul style="list-style-type: none">• Allowed the inclusion of patients with Smith-Magenis Syndrome, SH2B1 haploinsufficiency Carboxypeptidase E Deficiency and Leptin Deficiency Obesity.• Removed the option to use placebo to practice the injection technique during screening.• Removed the option for clinic visits to be performed by a home health care professional at the patient's home for Visits 4, 11 and 13.• Remove the optional sub-study of serial photography.• Added a screening assessment to review the specific genetic mutation for the patient to ensure eligibility.• Added guidance that blood draws could be prioritised if venous access was compromised due to the extreme obesity seen in these patients.• Added exposure and safety data for patients treated at the 3.0 mg dose.• Clarified the collection schedule for anti-RM-493 antibodies.

31 May 2019	<p>Amendment 9.0</p> <ul style="list-style-type: none"> • Protocol Amendment 9 was completely reformatted and reorganised, using an electronic StartingPoint Submission Authoring Template. • Study Objectives <ul style="list-style-type: none"> o Decreased number of specific objectives. o Rearranged objectives into primary, secondary, and exploratory only; none are designated tertiary. o Eliminated secondary objectives for patients who continue into the long-term extension – extension was changed to be a separate protocol. o Deleted secondary objectives related to diabetes, and all glucose parameters except HbA1c. o Added EuroQoL-Five Dimension assessments, SF-10 and SF-12 Surveys, and Patient-Reported Behavioral Disturbance Questionnaire. o Removed PedsQL and SF-36. • Study Endpoints <ul style="list-style-type: none"> o Changed primary endpoint from “The primary endpoint is the mean percent change from baseline in body weight at the end of ~3 months of treatment” to “The proportion of patients in each subgroup of RGDO who achieve at least 5% body weight reduction from baseline, at ~3 months treatment with setmelanotide.”
31 May 2019	<p>Amendment 9.0 Continued (1)</p> <ul style="list-style-type: none"> • Study Design <ul style="list-style-type: none"> o Revised the “dose titration” phase of the study to “dose escalation to a predetermined maximum.” New study design has only 1 escalation step (from 2.0 mg/day to 3.0 mg/day for patients ≥16 years of age) and 2 escalation steps (from 1.0 mg/day to 2.0 mg/day to 3.0 mg/day for patients 12 up to 15 years of age). Both age groups undergo a total of 16 weeks of treatment. Visit times were updated accordingly. o Changed length of treatment (10 weeks to 16 weeks) and number/frequency of visits, compared to Amendment 7. o Revised the end-of-study options for patients. In Amendment 7, some patients were eligible for 1-year extension, and others were withdrawn from study. In Amendment 9, patient can choose to either exit the current study or participate in a separate Extension Study Protocol. (If that study is not yet open at the site, patient can choose to continue treatment via Bridging Visits, and then enter the new extension study when it is available.) o Added directions for patients already enrolled in the study to transition to from dose titration to dose escalation o Reduced the number of available substudies to 1 o Modified process of Data Safety Monitoring (DSM). DSM was made the responsibility of the Investigator, on an ongoing basis, rather than an internal safety monitoring committee. Study was also monitored by a DSMB with outside advisers who met periodically.
31 May 2019	<p>Amendment 9.0 Continued (2)</p> <ul style="list-style-type: none"> • Study Population <ul style="list-style-type: none"> o Increased number of patients planned from “up to 80” to “approximately 150” patients o Modified Inclusion and Exclusion Criteria (removed BBS/AS patients and added 16P11.2 patients; also see Summary of Changes Amendment 7 to Amendment 9 in Appendix 16.1.1 for any additional changes) o Updated Withdrawal of Patients to reflect the new statement of the primary endpoint. • Study Treatments <ul style="list-style-type: none"> o Added updated description of study drug dosing and dosing schedule for 2 different age groups; the maximum dose for both age groups was 3.0 mg o Added more specifics concerning Treatment Compliance. o Removed discussion of permitted medications and information regarding procedures, and updated prohibited medications section.

31 May 2019	<p>Amendment 9.0 Continued (3)</p> <ul style="list-style-type: none"> • Schedule of Assessments / Patient Assessments and Requirements <ul style="list-style-type: none"> o Rearranged Schedule of Assessments (Table 3) to reflect the amended study design, and updated footnotes accordingly. o Rearranged descriptions of all assessments into one section rather than into groups by Efficacy vs. Clinical Procedures and Safety, and modified assessment descriptions to reflect changes in study design. o Pulled fasting lipids and HbA1C measurements out of Safety Labs group to be listed separately in the schedule of assessments. o Updated Safety Labs (called Clinical Labs in Amendment 7) to be performed in a central laboratory, rather than in local laboratories. o Added list of laboratory test priorities to be followed if the number of blood draws was too small to perform all laboratory tests. o Added EQ-5D assessments. o Added Patient-Reported Behavioral Disturbance Questionnaire. o Removed PedsQL and SF-36, and added SF-10 and SF-12. o Removed OGTT. o Grouped hs-CRP as part of hormonal activity group, removing it from the schedule of assessments. o Deleted optional substudies ABPM, quantitative skin colour assessment, and Energy Expenditure. ("Quantitative skin colour assessment" was part of the Comprehensive Skin Exam by dermatologist, and part of Fitzpatrick scale.) o Expanded description of ECG procedures. o Added section on Hepatic Fibrosis.
31 May 2019	<p>Amendment 9.0 Continued (4)</p> <ul style="list-style-type: none"> • Adverse Events <ul style="list-style-type: none"> o Revised AE reporting process: AEs were reported to Advanced Clinical and the email address was provided. o Added sections to describe Assessment of Severity and relationship to study drug, and expanded the information in the AE section overall. Also added the statement, "Any elevation in PHQ-9 or C-SSRS score should be evaluated to determine whether it meets the criteria for reporting as an AE." • Data Analysis/Statistical Procedures <ul style="list-style-type: none"> o Updated statements of primary objective and primary endpoint. o Stated that no formal hypothesis would be tested. • Administrative Requirements <ul style="list-style-type: none"> o Removed discussion of Long-Term Extensions and Pooling of Patients with the same rare genetic obesity population from other studies. o Deleted "Publication is likely to be coordinated with the investigators of RM-493-011, a sister protocol to this study ongoing in Germany with similar design and patient populations." • Appendices <ul style="list-style-type: none"> o Appendix C: Added last sentence "Menarche history will be obtained for females." o Removed "Evaluation of Abnormal Liver Function Tests (LFTs)" and all dose titration guidelines. o Removed the reproduction of "World Medical Association Declaration of Helsinki."

20 February 2020	<p>Amendment 10.0</p> <ul style="list-style-type: none"> • Added that study centres from the Middle East would be included in the study • Modified the exploratory objective and endpoints to remove hormonal assays • Lowered the age of inclusion from 12 to 6 years old • Removed bone density from the exploratory endpoints • Added that enrolment could be temporarily held • Added that the study number (014) would be the first 3 digits of the patient identification number • Changed screening window from 6 to 8 weeks • Section on hunger assessments was rearranged to more clearly describe the various hunger questionnaires used in the study • For Quality of Life / Mental Health Assessments, a clarifying statement was added to specify that if a patient's age changed while enrolled into the clinical study, he/she should continue to complete the same version of the instrument that they had been using previously. • For the EuroQoL-Five Dimension assessment, a statement was added to specify that patients between the ages of 6 and 8 years old would not take the assessment. • The following were specified as the biomarkers to be assayed: thyroid stimulating hormone (TSH), free thyroxine (T4), leptin, insulin, and high-sensitivity C-reactive protein (hs-CRP)
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported