



Clinical trial results:

Title: A 2-Stage (Open-Label Run-in followed by Randomized Withdrawal), Double-Blind, Placebo-Controlled, Phase 2 study of Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway

Trial design: This was a 2-stage, Phase 2 study of setmelanotide in patients with obesity with specific gene variants in the melanocortin 4 receptor (MC4R) pathway, with a 16-week open-label treatment stage followed by a 24-week randomized, double-blind, placebo-controlled stage. The primary objective was to evaluate the proportion of patients who achieved a clinically meaningful reduction in body weight in response to setmelanotide at the end of open-label treatment.

During Stage 1, setmelanotide was administered subcutaneously once daily (QD). For patients ≥ 12 years of age, the starting dose of setmelanotide was 2 mg QD for approximately 2 weeks then increased to 3 mg QD. For patients 6 to <12 years of age, the starting dose was 1 mg QD for approximately 1 week, increased to 2 mg QD for approximately 1 week, and then increased to 3 mg QD.

To be eligible to enter Stage 2 of the study, a patient aged ≥ 18 years had to achieve a body mass index (BMI) at least 3% less than at baseline at the end of Stage 1. A patient <18 years old had to achieve a BMI at least 3% less than at baseline or a decrease in BMI Z-score of at least 0.05 at the end of Stage 1. All patients eligible for Stage 2 were randomized 2:1 to either continue setmelanotide or receive matching placebo.

Overall 164 patients were treated with study drug in Stage 1, with a mean duration of treatment of 86 days (range: 1 to 140 days). In Stage 2, a total of 49 patients received study drug with a mean duration of treatment of 140.6 days (range: 9 to 197 days).

Summary

EudraCT number	2021-002855-12
Trial protocol	FR DE ES NL GR
Global end of trial date	30 September 2024

Results information

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

Trial information

Trial identification

Sponsor protocol code	RM-493-034
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04963231
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., +1 857 264 4280, clinicaltrials@rhythmtx.com
Scientific contact	Rhythm Clinical Trials, Rhythm Pharmaceuticals Inc., +1 857 264 4280, clinicaltrials@rhythmtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	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	30 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2024
Global end of trial reached?	Yes
Global end of trial date	30 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the proportion of obese patients with genetic defects in the melanocortin-4 receptor (MC4R) pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide after an initial response to open-label treatment.

Protection of trial subjects:

The Institutional Review Boards (IRB)/Independent Ethics Committees (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/assent was obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent complied with ICH-GCP and all applicable regulatory requirement(s).

Background therapy:

Medication that was considered necessary for the patient's safety and wellbeing was given during the study at the discretion of the treating physician after discussion with the Medical Monitor. All concomitant medications were kept at a stable dose throughout the course of the study, unless a dose change was necessary due to an AE. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient was receiving at the time of enrolment or received during the study was recorded along with the:

- Reason for use
 - Dates of administration including start and end dates
 - Dosage information including dose and frequency
- GLP 1 receptor agonists and anti-obesity medications were permitted as long as:
- the regimen and/or dose had been stable for at least 3 months prior to randomization
 - the patient had not experienced weight loss $\geq 2\%$ during the previous 3 months, AND
 - the patient intended to keep the regimen and/or dose stable throughout the course of the study.

The Sponsor was contacted if there were any questions regarding concomitant or prior therapy.

Evidence for comparator: -

Actual start date of recruitment	29 November 2021
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	United States: 100
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	164
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	23
Adolescents (12-17 years)	32
Adults (18-64 years)	109
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

164 patients with rare genetic disorders of obesity (RGDO) were recruited in Canada, Europe, Israel, and the USA from 29 Nov 2021 (first dose 13 Jan 2022). Patients were between 6 - 65 years with a genetically confirmed variant in an established MC4R pathway gene contributing to obesity. The last patient last visit for the analysis was 14 Feb 2024.

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	Stage 1 - Open Label
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable; Stage 1 was open-label.

Arms

Arm title	Stage 1 - Setmelanotide
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Arm description:

This was a 16 week open-label treatment stage in which all patients with RGDO were treated with setmelanotide.

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:

For patients 12 years or older, the starting dose was 2 mg QD for approximately 2 weeks after which it was increased to 3 mg QD. Dose escalation occurred at the study visit planned for Day 14 (± 3 days) and occurred on the day of that visit.

If the starting dose was not tolerated, the dose was reduced to 1 mg QD, which was the lowest target dose in patients ≥ 12 years of age; however, in consultation with the medical monitor, the dose could be lowered to 0.5 mg QD if not tolerated.

For patients 6 to <12 years old, the starting dose was 1 mg QD for approximately 1 week, then increased to 2 mg QD for approximately 1 week, and then increased to 3 mg QD. Dose escalation occurred during the phone call planned for Day 7 (± 2 days) and on the day of the study visit planned for Day 14 (± 3 days).

If the starting dose was not tolerated, the dose was reduced to 0.5 mg QD, the lowest target dose in patients 6 - 12 years old.

All study patients received study drug by SC injection QD.

Number of subjects in period 1	Stage 1 - Setmelanotide
Started	164
Completed	100
Not completed	64
Consent withdrawn by subject	16
Adverse event, non-fatal	43
Lost to follow-up	2
Protocol deviation	3

Period 2

Period 2 title	Stage 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Stage 1 of the trial is open-label. Patients who are eligible to enter Stage 2 of the trial will be randomized in a blinded manner at the Stage 2 Entry Visit in a 2:1 ratio to receive either setmelanotide (2) or placebo (1). Stratification by gene cohort occurred for specific genes being enrolled into this trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Eligible patients who entered Stage 2 continued in the study for an additional 24 weeks. Eligible patients were randomized 2:1 to either continue QD setmelanotide or receive matching placebo. Patients in this arm received placebo.

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

Dosage and administration details:

All study patients received study drug by SC injection QD (administered in the morning).

Arm title	Setmelanotide
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Arm description:

Eligible patients who entered Stage 2 continued in the study for an additional 24 weeks. Eligible patients were randomized 2:1 to either continue QD setmelanotide or receive matching placebo. Patients in this arm received QD setmelanotide.

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:

For patients 12 years or older, the starting dose was 2 mg QD for approximately 2 weeks after which it was increased to 3 mg QD. Dose escalation occurred at the study visit planned for Day 14 (± 3 days) and occurred on the day of that visit.

If the starting dose was not tolerated, the dose was reduced to 1 mg QD, which was the lowest target dose in patients ≥ 12 years of age; however, in consultation with the medical monitor, the dose could be lowered to 0.5 mg QD if not tolerated.

For patients 6 to <12 years old, the starting dose was 1 mg QD for approximately 1 week, then increased to 2 mg QD for approximately 1 week, and then increased to 3 mg QD. Dose escalation occurred during the phone call planned for Day 7 (± 2 days) and on the day of the study visit planned for Day 14 (± 3 days).

If the starting dose was not tolerated, the dose was reduced to 0.5 mg QD, the lowest target dose in patients 6 - 12 years old.

All study patients received study drug by SC injection QD.

Number of subjects in period 2 ^[1]	Placebo	Setmelanotide
Started	17	32
Completed	10	29
Not completed	7	3
Other than specified above	-	1
Consent withdrawn by subject	2	2
Other than reasons specified above	4	-
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Eligibility for participation in Stage 2 was dependent on achieving a pre-specified reduction in BMI or BMI Z-score at the end of Stage 1.

Baseline characteristics

Reporting groups

Reporting group title	Stage 1 - Open Label
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Reporting group description: -

Reporting group values	Stage 1 - Open Label	Total	
Number of subjects	164	164	
Age categorical			
Units: Subjects			
Children (2-11 years)	23	23	
Adolescents (12-17 years)	32	32	
Adults (18-64 years)	109	109	
Age continuous			
Units: years			
arithmetic mean	30.2		
standard deviation	± 16.94	-	
Gender categorical			
Units: Subjects			
Female	110	110	
Male	54	54	
Baseline BMI			
Units: kg/m2			
arithmetic mean	45.3		
standard deviation	± 9.55	-	
Baseline waist circumference			
Units: centimetre			
arithmetic mean	126.8		
standard deviation	± 22.04	-	

Subject analysis sets

Subject analysis set title	SEMA3 Path
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Genetic cohort including patients with mutations in the SEMA3 Path

Subject analysis set title	PHIP
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Genetic cohort including patients with mutations in PHIP

Subject analysis set title	SIM1
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Genetic cohort including patients with mutations in SIM1

Subject analysis set title	MAGEL2
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Genetic cohort including patients with mutations in MAGEL2

Subject analysis set title	Other
Subject analysis set type	Safety analysis

Subject analysis set description:

Note that there is also a genetic cohort identified as "other"; however, efficacy data were not pooled across the genes within this cohort.

Reporting group values	SEMA3 Path	PHIP	SIM1
Number of subjects	90	16	20
Age categorical Units: Subjects			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
Age continuous Units: years			
arithmetic mean	31.1	26.6	28.5
standard deviation	± 17.69	± 16.59	± 13.45
Gender categorical Units: Subjects			
Female	60	8	15
Male	30	8	5
Baseline BMI Units: kg/m2			
arithmetic mean	45.52	40.8	47.7
standard deviation	± 8.76	± 10.02	± 9.73
Baseline waist circumference Units: centimetre			
arithmetic mean	127.5	119.7	128.5
standard deviation	± 20.23	± 25.44	± 23.47

Reporting group values	MAGEL2	Other	
Number of subjects	10	28	
Age categorical Units: Subjects			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
Age continuous Units: years			
arithmetic mean	32.4	29.8	
standard deviation	± 19.01	± 16.87	
Gender categorical Units: Subjects			
Female	8	19	
Male	2	9	
Baseline BMI Units: kg/m2			
arithmetic mean	42.1	46.8	
standard deviation	± 8.26	± 11.39	
Baseline waist circumference Units: centimetre			
arithmetic mean	125.9	127.8	

standard deviation	± 26.81	± 23.71	
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End points

End points reporting groups

Reporting group title	Stage 1 - Setmelanotide
Reporting group description: This was a 16 week open-label treatment stage in which all patients with RGDO were treated with setmelanotide.	
Reporting group title	Placebo
Reporting group description: Eligible patients who entered Stage 2 continued in the study for an additional 24 weeks. Eligible patients were randomized 2:1 to either continue QD setmelanotide or receive matching placebo. Patients in this arm received placebo.	
Reporting group title	Setmelanotide
Reporting group description: Eligible patients who entered Stage 2 continued in the study for an additional 24 weeks. Eligible patients were randomized 2:1 to either continue QD setmelanotide or receive matching placebo. Patients in this arm received QD setmelanotide.	
Subject analysis set title	SEMA3 Path
Subject analysis set type	Safety analysis
Subject analysis set description: Genetic cohort including patients with mutations in the SEMA3 Path	
Subject analysis set title	PHIP
Subject analysis set type	Safety analysis
Subject analysis set description: Genetic cohort including patients with mutations in PHIP	
Subject analysis set title	SIM1
Subject analysis set type	Safety analysis
Subject analysis set description: Genetic cohort including patients with mutations in SIM1	
Subject analysis set title	MAGEL2
Subject analysis set type	Safety analysis
Subject analysis set description: Genetic cohort including patients with mutations in MAGEL2	
Subject analysis set title	Other
Subject analysis set type	Safety analysis
Subject analysis set description: Note that there is also a genetic cohort identified as "other"; however, efficacy data were not pooled across the genes within this cohort.	

Primary: Proportion of Patients who Achieved a $\geq 5\%$ Reduction in BMI from Baseline at Week 16 (End of Stage 1)

End point title	Proportion of Patients who Achieved a $\geq 5\%$ Reduction in BMI from Baseline at Week 16 (End of Stage 1) ^[1]
End point description: To evaluate the proportion of patients with obesity and genetic variants in the MC4R pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide	
End point type	Primary
End point timeframe: Baseline to End of Stage 1 (16 weeks)	

Notes:

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

Justification: This was not a comparator study. For the analysis of Proportion of Patients who Achieved a $\geq 5\%$ Reduction in BMI from Baseline, percent changes in BMI from baseline over time were

summarized using descriptive statistics.

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	164	90	16	20
Units: percent				
number (confidence interval 95%)	29.9 (23.0 to 37.5)	31.1 (21.8 to 41.7)	56.3 (29.9 to 80.2)	25.0 (8.7 to 49.1)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percent				
number (confidence interval 95%)	30.0 (6.7 to 65.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in BMI from Baseline to the End of Stage 1 - All Patients

End point title	Mean Change in BMI from Baseline to the End of Stage 1 - All Patients
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End point description:

To evaluate change in weight parameters in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of Stage 1 (16 weeks)

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	58	13	16
Units: kg/m2				
arithmetic mean (standard deviation)	-1.92 (± 1.79)	-2.19 (± 2.02)	-2.12 (± 1.01)	-1.70 (± 1.89)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	7			

Units: kg/m2				
arithmetic mean (standard deviation)	-1.64 (± 1.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in BMI from Baseline to the End of Stage 1 - All patients

End point title	Percent Change in BMI from Baseline to the End of Stage 1 - All patients
End point description: To evaluate change in weight parameters in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.	
End point type	Secondary
End point timeframe: Baseline to end of Stage 1 (16 weeks)	

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	58	13	16
Units: percent				
arithmetic mean (standard deviation)	-4.62 (± 4.39)	-4.98 (± 4.47)	-6.12 (± 3.62)	-4.02 (± 5.31)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (standard deviation)	-4.60 (± 4.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in BMI from Baseline to the End of Stage 1; Patients ≥18 Years

End point title	Mean Change in BMI from Baseline to the End of Stage 1; Patients ≥18 Years
End point description: To evaluate change in weight parameters in response to setmelanotide in patients ≥18 years old with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.	
End point type	Secondary

End point timeframe:

Baseline to end of Stage 1 (16 weeks)

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	36	7	10
Units: kg/m2				
arithmetic mean (standard deviation)	-1.87 (± 1.89)	-2.36 (± 2.12)	-2.11 (± 1.14)	-1.47 (± 1.79)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: kg/m2				
arithmetic mean (standard deviation)	-1.19 (± 1.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in BMI from Baseline to the End of Stage 1; Patients ≥18 Years

End point title	Percent Change in BMI from Baseline to the End of Stage 1; Patients ≥18 Years
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End point description:

To evaluate change in weight parameters in response to setmelanotide in patients ≥18 years old with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of Stage 1 (16 weeks)

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	36	7	10
Units: percent				
arithmetic mean (standard deviation)	-3.95 (± 4.05)	-4.96 (± 4.47)	-5.11 (± 2.77)	-2.63 (± 3.72)

End point values	MAGEL2			
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Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: percent				
arithmetic mean (standard deviation)	-2.67 (\pm 2.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Body Weight from Baseline to the End of Stage 1; Patients \geq 18 Years

End point title	Mean Change in Body Weight from Baseline to the End of Stage 1; Patients \geq 18 Years
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to end of Stage 1 (16 weeks(

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	36	7	10
Units: kilogram(s)				
arithmetic mean (standard deviation)	-5.33 (\pm 5.31)	-6.77 (\pm 5.91)	-5.77 (\pm 3.50)	-4.13 (\pm 4.72)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: kilogram(s)				
arithmetic mean (standard deviation)	-3.88 (\pm 3.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Body Weight from Baseline to the End of Stage 1; Patients \geq 18 Years

End point title	Percent Change in Body Weight from Baseline to the End of Stage 1; Patients \geq 18 Years
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to end of Stage 1 (16 weeks)	

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	36	7	10
Units: percent				
arithmetic mean (standard deviation)	-3.94 (± 4.05)	-4.96 (± 4.47)	-5.00 (± 2.74)	-2.63 (± 3.72)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: percent				
arithmetic mean (standard deviation)	-2.67 (± 2.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in BMI Z-score from Baseline to the End of Stage 1; Patients <18 Years

End point title	Mean Change in BMI Z-score from Baseline to the End of Stage 1; Patients <18 Years
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End point description:

To evaluate change in weight parameters in patients less than 18 years of age in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.

End point type	Secondary
End point timeframe:	
Baseline to end of Stage 1 (16 weeks)	

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	22	6	6
Units: Z-score				
arithmetic mean (standard deviation)	-0.13 (± 0.14)	-0.09 (± 0.08)	-0.20 (± 0.19)	-0.18 (± 0.23)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Z-score				
arithmetic mean (standard deviation)	-0.18 (± 0.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Weekly Average of the daily Maximal Hunger Score from Baseline to the End of Stage 1; Patients ≥12 Years

End point title	Mean Change in Weekly Average of the daily Maximal Hunger Score from Baseline to the End of Stage 1; Patients ≥12 Years
End point description: To evaluate change in hunger in response to setmelanotide in patients ≥12 years old with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.	
End point type	Secondary
End point timeframe: Baseline to end of Stage 1 (16 weeks)	

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	38	8	14
Units: Hunger Score				
arithmetic mean (standard deviation)	-2.56 (± 2.26)	-2.35 (± 2.43)	-3.87 (± 1.41)	-1.91 (± 2.38)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Hunger Score				
arithmetic mean (standard deviation)	-3.28 (± 2.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Weekly Average of the daily Maximal Hunger Score from Baseline to the End of Stage 1; Patients ≥12 Years

End point title	Percent Change in Weekly Average of the daily Maximal Hunger Score from Baseline to the End of Stage 1; Patients ≥12 Years
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End point description:

To evaluate change in hunger in response to setmelanotide in patients ≥ 12 years old with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment.

End point type	Secondary
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End point timeframe:

Baseline to end of Stage 1 (16 weeks)

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	38	8	14
Units: percent				
arithmetic mean (standard deviation)	-31.13 (\pm 63.27)	-23.70 (\pm 81.93)	-56.87 (\pm 19.46)	-25.60 (\pm 51.69)

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: percent				
arithmetic mean (standard deviation)	-39.44 (\pm 30.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Proportion of Patients ≥ 12 Years Old, Per Gene, Who Achieve a ≥ 2 Point Reduction in the Weekly Average of the Daily Maximal Hunger Score

End point title	The Proportion of Patients ≥ 12 Years Old, Per Gene, Who Achieve a ≥ 2 Point Reduction in the Weekly Average of the Daily Maximal Hunger Score
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End point description:

The proportion of patients ≥ 12 years old, per gene, who achieve a ≥ 2 point reduction (improvement) in the weekly average of the daily maximal hunger score.

End point type	Secondary
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End point timeframe:

Baseline to end of Stage 1 (16 weeks)

End point values	Stage 1 - Setmelanotide	SEMA3 Path	PHIP	SIM1
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	141	77	12	20
Units: Patients				
Patients Achieving a ≥ 2 Point Reduction	49	22	7	7
Patients Not Achieving a ≥ 2 Point Reduction	92	55	5	13

End point values	MAGEL2			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Patients				
Patients Achieving a ≥ 2 Point Reduction	5			
Patients Not Achieving a ≥ 2 Point Reduction	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of Stage 2

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Stage 1 - All patients
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Reporting group description:

All 164 patients received at least 1 dose of setmelanotide in Stage 1, and therefore, comprise the Safety Analysis Set.

Reporting group title	Stage 2 - Setmelanotide
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Reporting group description:

Note, 3 patients randomised to placebo were rescued with open-label setmelanotide during Stage 2. They were analysed for safety with the setmelanotide group.

Reporting group title	Stage 2 - Placebo
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Reporting group description:

Note, 3 patients randomised to placebo were rescued with open-label setmelanotide during Stage 2. They were analysed for safety with the setmelanotide group.

Serious adverse events	Stage 1 - All patients	Stage 2 - Setmelanotide	Stage 2 - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 164 (3.66%)	0 / 35 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 164 (0.61%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 164 (0.61%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 164 (0.61%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 164 (1.22%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Stage 1 - All patients	Stage 2 - Setmelanotide	Stage 2 - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 164 (97.56%)	25 / 35 (71.43%)	10 / 14 (71.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	52 / 164 (31.71%)	7 / 35 (20.00%)	2 / 14 (14.29%)
occurrences (all)	100	10	5
Nervous system disorders			
Headache			
subjects affected / exposed	43 / 164 (26.22%)	4 / 35 (11.43%)	0 / 14 (0.00%)
occurrences (all)	60	6	0
Dizziness			
subjects affected / exposed	8 / 164 (4.88%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	11	1	0

General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	62 / 164 (37.80%)	1 / 35 (2.86%)	2 / 14 (14.29%)
occurrences (all)	164	4	2
Injection site pain			
subjects affected / exposed	46 / 164 (28.05%)	0 / 35 (0.00%)	1 / 14 (7.14%)
occurrences (all)	99	0	1
Injection site induration			
subjects affected / exposed	47 / 164 (28.66%)	1 / 35 (2.86%)	2 / 14 (14.29%)
occurrences (all)	90	1	2
Injection site pruritus			
subjects affected / exposed	49 / 164 (29.88%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	62	1	0
Fatigue			
subjects affected / exposed	29 / 164 (17.68%)	0 / 35 (0.00%)	1 / 14 (7.14%)
occurrences (all)	35	0	1
Injection site oedema			
subjects affected / exposed	20 / 164 (12.20%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	35	1	0
Injection site bruising			
subjects affected / exposed	22 / 164 (13.41%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	25	0	0
Injection site reaction			
subjects affected / exposed	9 / 164 (5.49%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	16	1	0
Injection site discolouration			
subjects affected / exposed	10 / 164 (6.10%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	10	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	75 / 164 (45.73%)	4 / 35 (11.43%)	0 / 14 (0.00%)
occurrences (all)	89	4	0
Vomiting			
subjects affected / exposed	41 / 164 (25.00%)	3 / 35 (8.57%)	0 / 14 (0.00%)
occurrences (all)	48	3	0
Diarrhoea			

subjects affected / exposed	22 / 164 (13.41%)	2 / 35 (5.71%)	0 / 14 (0.00%)
occurrences (all)	25	2	0
Abdominal pain			
subjects affected / exposed	13 / 164 (7.93%)	2 / 35 (5.71%)	2 / 14 (14.29%)
occurrences (all)	14	2	2
Pigmentation lip			
subjects affected / exposed	9 / 164 (5.49%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	9	1	0
Constipation			
subjects affected / exposed	4 / 164 (2.44%)	2 / 35 (5.71%)	2 / 14 (14.29%)
occurrences (all)	4	3	2
Reproductive system and breast disorders			
Vulvovaginal discomfort			
subjects affected / exposed	10 / 164 (6.10%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	10	0	0
Spontaneous penile erection			
subjects affected / exposed	6 / 164 (3.66%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	7	0	0
Erection increased			
subjects affected / exposed	4 / 164 (2.44%)	1 / 35 (2.86%)	0 / 14 (0.00%)
occurrences (all)	5	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 164 (7.93%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	16	0	0
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	130 / 164 (79.27%)	7 / 35 (20.00%)	1 / 14 (7.14%)
occurrences (all)	286	8	2
Pruritus			
subjects affected / exposed	11 / 164 (6.71%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	11	0	0
Rash			
subjects affected / exposed	10 / 164 (6.10%)	0 / 35 (0.00%)	0 / 14 (0.00%)
occurrences (all)	10	0	0
Skin discolouration			

subjects affected / exposed occurrences (all)	1 / 164 (0.61%) 1	1 / 35 (2.86%) 1	2 / 14 (14.29%) 2
Psychiatric disorders Libido increased subjects affected / exposed occurrences (all)	15 / 164 (9.15%) 15	0 / 35 (0.00%) 0	0 / 14 (0.00%) 0
Disturbance in sexual arousal subjects affected / exposed occurrences (all)	11 / 164 (6.71%) 12	0 / 35 (0.00%) 0	0 / 14 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 164 (8.54%) 15	4 / 35 (11.43%) 4	1 / 14 (7.14%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2022	Protocol Version 2.0: <ul style="list-style-type: none">• Reduced sample size and target number of patients per gene• Changed primary endpoint to proportion of patients who were responders following open-label treatment with setmelanotide at the end of Stage 1; revised primary objective, accordingly.• Moved safety objective and endpoint from secondary to its own safety section.• Changed the weight- and hunger-related secondary objective and endpoints to be determined per gene.
27 July 2022	Protocol Version 2.0 continued (1): <ul style="list-style-type: none">• Changed criterion to enter Stage 2 of the trial.• Changed criterion to receive "rescue" treatment with open-label setmelanotide in Stage 2 and changed rescue treatment to be provided as part of either a LTE study or through BVs.• Added the following inclusion criterion: Symptoms or behaviours of hyperphagia persistent during the patient's life, including manifestations in childhood, as determined by the Investigator at screening• Changed the exclusion criterion to weight loss >2% within the previous 3 months and permitted the use of stable dietary and/or exercise regimens, or medications, supplements or herbal treatment used for weight maintenance or to prevent weight gain (including GLP 1 receptor agonists)• Added an exclusion criterion regarding the following genetic variants: biallelic BBS; biallelic ALMS1; homozygous, heterozygous, or compound heterozygous variants in MC4R, POMC, PCSK1, LEPR, NCOA1; SRC1 or SH2B1 genes as well as 16p11.2 chromosomal deletions that include the SH2B1 gene
27 July 2022	Protocol Version 2.0 continued (2): <ul style="list-style-type: none">• Changed GFR exclusion criterion to eGFR <30 mL/min/1.73 m² (per the MDRD equation in patients ≥18 years of age and per the bedside Schwartz equation in patients <18 years of age)• Permitted treatment discontinuation without withdrawal from the study• Added sections for "lost to follow-up," "skin protection," "drug interruption and stopping rules," "biomarkers," and "ADA"• Permitted dose reductions in the event the drug was not well-tolerated• Added fasting glucose to metabolic parameters• Updated analysis of the primary efficacy endpoint (based on revised endpoint)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported