



Clinical trial results:

Title: A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) With a Crossover to Open Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation.

Trial design: This was a double-blind, double-dummy, randomised, crossover to open-label, multicentre study designed to compare the PK, safety, and efficacy of the QW (once weekly) and QD (once daily) subcutaneous (SC) formulations of setmelanotide, as well as the safety and efficacy after 6 months of QW setmelanotide in patients with BBS, biallelic PPL, or heterozygous PPL. In total, 19 patients, aged 8 to 37 years, who had taken QD setmelanotide in trial RM-493-022 (long-term extension [LTE] trial) for at least 6 months with acceptable safety and tolerability were treated.

At screening, a daily hunger questionnaire and medical evaluation were completed, followed by a run-in period on QD setmelanotide at the dose they were taking in the LTE trial.

On Day 1 (Visit 3), patients were randomised 1:1 to receive either QD or QW setmelanotide. Patients on QD 2 mg dose in the LTE trial were randomised to either QD 2 mg or QW 20 mg setmelanotide, patients on QD 2.5 mg to either QD 2.5 mg or QW 25 mg setmelanotide, and patients on QD 3 mg to either QD 3 mg or QW 30 mg setmelanotide. Double-blind conditions were maintained via placebo (dummy) SC injections. From Week 14, all patients crossed over to a 13-week open-label treatment period with QW setmelanotide.

Thereafter, in a 3-week follow-up period, all patients returned to their run-in dose of QD setmelanotide.

Overall, the median duration of treatment was 29.14 weeks (range: 1.3 to 30.3 weeks) and was similar in both arms.

The primary endpoint was the comparison of steady state PK parameters (C_{max}, T_{max}, C_{trough}, and AUC_{0-tau}) for the QD and QW formulations of setmelanotide.

Summary

EudraCT number	2021-004597-65
Trial protocol	NL DE
Global end of trial date	19 October 2023

Results information

Result version number	v1 (current)
This version publication date	05 July 2024
First version publication date	05 July 2024

Trial information

Trial identification

Sponsor protocol code	RM-493-037
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05194124
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	Physician Inquiry 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	19 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2023
Global end of trial reached?	Yes
Global end of trial date	19 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pharmacokinetics (PK) of the once daily (QD) and once weekly (QW) formulations of setmelanotide

Protection of trial subjects:

The Institutional Review Board (IRB) 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.
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Background therapy:

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:

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

GLP 1 receptor agonists could be used up to the dose approved for the treatment of diabetes mellitus (eg, liraglutide up to a daily dose of 1.8 mg) as long as (1) it was not being prescribed for the treatment of obesity, (2) the dose had been stable for at least 3 months prior to enrolment, (3) the patient had not experienced >3% weight loss during the previous 3 months, AND (4) the patient intended to keep the dose stable throughout the course of the study.

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

Medications that are approved to treat obesity (eg, orlistat, lorcaserin, phentermine-topiramate, and naltrexone-bupropion) were not allowed within 3 months prior to the first dose of study medication (eg, enrolment) and were prohibited during the study. GLP-1 receptor agonists being prescribed for the treatment of obesity were not allowed.

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 AE.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	20 December 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	Netherlands: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	19
EEA total number of subjects	5

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)	2
Adolescents (12-17 years)	7
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited 19 patients with rare genetic disorders of obesity (RGDO) in Canada, Europe, Puerto Rico, and the United States from 20 Dec 2019 (first dose 05 Jan 2022). Eligible patients had been treated for at least 6 months with QD setmelanotide in trial RM-493-022. The last patient last visit was 19 Oct 2023.

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	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To maintain the blind during the 13-week randomised treatment period, all patients received placebo injections (mPEG-DSPE vehicle for the QD formulation or FluidCrystal vehicle for the QW formulation) in addition to the setmelanotide injections in a double-dummy fashion.

Blinded randomisation occurred via an IRT system.

Arms

Are arms mutually exclusive?	Yes
Arm title	QD Setmelanotide (baseline to Week 14)

Arm description:

The QD Setmelanotide group includes those patients who were randomised to QD setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.

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

Dosage and administration details:

Setmelanotide QD drug product (in mPEG-DSPE vehicle) was provided as a sterile solution at a concentration of 10 mg/mL for administration of dose levels of 2 mg, 2.5 mg, and 3 mg by SC injection.

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

Dosage and administration details:

The placebo for the QD formulation consists of the vehicle only (no active ingredient), was visually indistinguishable from the drug product.

Arm title	QW Setmelanotide (baseline to Week 14)
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Arm description:

The QW Setmelanotide group includes those patients randomised to QW setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.

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

Dosage and administration details:

The setmelanotide QW formulation (in FluidCrystal® vehicle) was provided as a sterile solution at a concentration of 30 mg/mL for administration of dose levels of 20 mg, 25 mg, and 30 mg by SC injection. Setmelanotide QW drug product consists of setmelanotide dissolved in a liquid lipid phase containing key excipients, soy phosphatidylcholine, and glycerol dioleate.

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

Dosage and administration details:

The placebo for the QW formulation consists of the vehicle only (no active ingredient) and was visually indistinguishable from the QW drug product.

Number of subjects in period 1	QD Setmelanotide (baseline to Week 14)	QW Setmelanotide (baseline to Week 14)
Started	9	10
Completed	6	9
Not completed	3	1
Adverse event, non-fatal	1	-
Withdrawal by Parent/ Guardian	2	1

Baseline characteristics

Reporting groups

Reporting group title	QD Setmelanotide (baseline to Week 14)
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Reporting group description:

The QD Setmelanotide group includes those patients who were randomised to QD setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.

Reporting group title	QW Setmelanotide (baseline to Week 14)
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Reporting group description:

The QW Setmelanotide group includes those patients randomised to QW setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.

Reporting group values	QD Setmelanotide (baseline to Week 14)	QW Setmelanotide (baseline to Week 14)	Total
Number of subjects	9	10	19
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	19.6 ± 8.23	21.5 ± 8.42	-
Gender categorical Units: Subjects			
Female	7	4	11
Male	2	6	8
Weight at baseline			
The most recent weight measurement prior to the first administration of study drug.			
Units: kilogram(s) arithmetic mean standard deviation	122.20 ± 32.045	98.73 ± 21.898	-
BMI at baseline			
The most recent body mass index (BMI) measurement prior to the first administration of study drug.			
Units: kg/m2 arithmetic mean standard deviation	42.491 ± 10.2494	34.598 ± 6.3978	-
Waist circumference at baseline			
The most recent waist circumference measurement prior to the first administration of study drug.			
Units: centimetre arithmetic mean standard deviation	113.79 ± 19.142	105.32 ± 16.437	-
BMI Z-score at baseline			
BMI Z-score is a measure of how many standard deviations a child or young person's BMI is above or below the average BMI for their age and gender.			
Units: Z-score arithmetic mean standard deviation	3.786 ± 1.3269	3.115 ± 1.0146	-

End points

End points reporting groups

Reporting group title	QD Setmelanotide (baseline to Week 14)
Reporting group description: The QD Setmelanotide group includes those patients who were randomised to QD setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.	
Reporting group title	QW Setmelanotide (baseline to Week 14)
Reporting group description: The QW Setmelanotide group includes those patients randomised to QW setmelanotide in the randomised double-blind treatment period. Patients were treated from baseline to Week 14.	
Subject analysis set title	QD Regimen - 2.0 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD Regimen - 2.0 mg dose.	
Subject analysis set title	QD Regimen - 2.5 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD Regimen - 2.5 mg dose	
Subject analysis set title	QD Regimen - 3.0 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD Regimen - 3.0 mg dose	
Subject analysis set title	QD-QW-QW Sequence - 20 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD-QW-QW Sequence - 20 mg dose	
Subject analysis set title	QD-QW-QW Sequence - 25 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD-QW-QW Sequence - 25 mg dose	
Subject analysis set title	QD-QD-QW Sequence - 30 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD-QD-QW Sequence - 30 mg dose	
Subject analysis set title	QD-QW-QW Sequence - 30 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD-QW-QW Sequence - 30 mg dose	
Subject analysis set title	QD-QD-QW Sequence - 3.0 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: QD-QD-QW Sequence - 3.0 mg dose	

Primary: Tmax (Visit 2)

End point title	Tmax (Visit 2) ^[1]
End point description: Time to reach maximum concentration in hours.	
End point type	Primary
End point timeframe: Visit 2	

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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD Regimen - 2.0 mg	QD Regimen - 2.5 mg	QD Regimen - 3.0 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	1	16	
Units: hour				
median (full range (min-max))	6.91 (5.92 to 7.90)	5.88 (5.88 to 5.88)	6.31 (2.00 to 8.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax (Visit 2)

End point title	Cmax (Visit 2) ^[2]
End point description:	Maximum concentration, determined directly from individual concentration–time data.
End point type	Primary
End point timeframe:	Visit 2

Notes:

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

Justification: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD Regimen - 2.0 mg	QD Regimen - 2.5 mg	QD Regimen - 3.0 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	1	16	
Units: ng/mL				
arithmetic mean (standard deviation)	29.4 (± 3.49)	44.8 (± 0)	59.9 (± 29.6)	

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-tau (Visit 2)

End point title	AUC 0-tau (Visit 2) ^[3]
End point description:	The area under the plasma concentration–time curve during the 24-hour (QD) or 168-hour (QW) dosing interval; calculated using the linear trapezoidal rule and allowing for interpolation/extrapolation to 24 hours/168 hours if applicable.
End point type	Primary

End point timeframe:

Visit 2

Notes:

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

Justification: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD Regimen - 2.0 mg	QD Regimen - 2.5 mg	QD Regimen - 3.0 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0 ^[4]	0 ^[5]	7	
Units: h*ng/mL				
arithmetic mean (standard deviation)	()	()	975 (± 659)	

Notes:

[4] - No samples were collected for this parameter with this group.

[5] - No samples were collected for this parameter with this group.

Statistical analyses

No statistical analyses for this end point

Primary: AUC last (Visit 2)

End point title	AUC last (Visit 2) ^[6]
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End point description:

Area under the concentration–time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal method.

End point type	Primary
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End point timeframe:

Visit 2

Notes:

[6] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD Regimen - 2.0 mg	QD Regimen - 2.5 mg	QD Regimen - 3.0 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	1	16	
Units: h*ng/mL				
arithmetic mean (standard deviation)	145 (± 24.6)	553 (± 0)	623 (± 539)	

Statistical analyses

No statistical analyses for this end point

Primary: Tmax (Visit 16)

End point title	Tmax (Visit 16) ^[7]
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End point description:

Time to reach maximum concentration in hours.

End point type	Primary
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End point timeframe:

Visit 16

Notes:

[7] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QD-QW Sequence - 30 mg	QD-QW-QW Sequence - 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	7	7
Units: hour				
median (full range (min-max))	3.93 (3.93 to 3.93)	5.93 (5.93 to 5.93)	3.05 (0.50 to 6.00)	4.85 (2.03 to 6.03)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax (Visit 16)

End point title Cmax (Visit 16)^[8]

End point description:

Maximum concentration, determined directly from individual concentration–time data.

End point type Primary

End point timeframe:

Visit 16

Notes:

[8] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QD-QW Sequence - 30 mg	QD-QW-QW Sequence - 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	7	7
Units: ng/mL				
arithmetic mean (standard deviation)	22.4 (± 0)	32.7 (± 0)	31.8 (± 28.6)	57.3 (± 33.0)

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-tau (Visit 16)

End point title AUC 0-tau (Visit 16)^[9]

End point description:

The area under the plasma concentration–time curve during the 24-hour (QD) or 168-hour (QW) dosing

interval; calculated using the linear trapezoidal rule and allowing for interpolation/extrapolation to 24 hours/168 hours if applicable.

End point type	Primary
End point timeframe:	
Visit 16	
Notes:	

[9] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QD-QW Sequence - 30 mg	QD-QW-QW Sequence - 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	6	6
Units: h*ng/mL				
arithmetic mean (standard deviation)	1590 (± 0)	2260 (± 0)	2470 (± 2890)	5010 (± 4000)

Statistical analyses

No statistical analyses for this end point

Primary: AUC last (Visit 16)

End point title	AUC last (Visit 16) ^[10]
End point description:	
Area under the concentration–time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal method.	
End point type	Primary
End point timeframe:	
Visit 16	

Notes:

[10] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QD-QW Sequence - 30 mg	QD-QW-QW Sequence - 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	7	7
Units: h*ng/mL				
arithmetic mean (standard deviation)	446 (± 0)	2260 (± 0)	1970 (± 2830)	3540 (± 3910)

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough (Visit 3)

End point title	Ctrough (Visit 3) ^[11]
End point description: Concentration at the end of the dosing interval, prior to subsequent dose administration.	
End point type	Primary
End point timeframe: Visit 3	

Notes:

[11] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QW-QW Sequence - 30 mg	QD-QD-QW Sequence - 3.0 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	1	7	9
Units: ng/mL				
arithmetic mean (standard deviation)	5.17 (± 0.856)	4.36 (± 0)	16.6 (± 16.3)	11.7 (± 13.5)

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough (Visit 7)

End point title	Ctrough (Visit 7) ^[12]
End point description: Concentration at the end of the dosing interval, prior to subsequent dose administration.	
End point type	Primary
End point timeframe: Visit 7	

Notes:

[12] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QW-QW Sequence - 30 mg	QD-QD-QW Sequence - 3.0 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[13]	1	7	7
Units: ng/mL				
arithmetic mean (standard deviation)	()	9.54 (± 0)	15.6 (± 13.3)	12.2 (± 7.62)

Notes:

[13] - No samples were collected for this endpoint in this group

Statistical analyses

No statistical analyses for this end point

Primary: Ctrough (Visit 11)

End point title	Ctrough (Visit 11) ^[14]
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End point description:

Concentration at the end of the dosing interval, prior to subsequent dose administration.

End point type	Primary
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End point timeframe:

Visit 11

Notes:

[14] - 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: The primary endpoints were PK parameters and the objective was to compare PK for the QD and QW formulations of setmelanotide. Each endpoint was reported with descriptive statistics only.

End point values	QD-QW-QW Sequence - 20 mg	QD-QW-QW Sequence - 25 mg	QD-QW-QW Sequence - 30 mg	QD-QD-QW Sequence - 3.0 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	6	7
Units: ng/mL				
arithmetic mean (standard deviation)	11.1 (± 0)	6.43 (± 0)	20.1 (± 13.7)	12.3 (± 11.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 26.

Adverse event reporting additional description:

The patients were randomised to and treated with QD or QW setmelanotide in a 13-week randomised double-blind treatment period. Thereafter, patients entered a 13-week, non-randomised, open-label treatment period during which all patients were treated with QW setmelanotide.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	QD Setmelanotide
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Reporting group description: -

Reporting group title	QW Setmelanotide
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Reporting group description: -

Serious adverse events	QD Setmelanotide	QW Setmelanotide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	QD Setmelanotide	QW Setmelanotide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	9 / 10 (90.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
General disorders and administration site conditions			

Injection site pain subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 11	6 / 10 (60.00%) 11	
Injection site erythema subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 6	4 / 10 (40.00%) 9	
Fatigue subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 10 (0.00%) 0	
Injection site induration subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	5 / 10 (50.00%) 10	
Injection site bruising subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 10 (10.00%) 2	
Injection site haemorrhage subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	3 / 10 (30.00%) 6	
Injection site pruritus subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	4 / 10 (40.00%) 5	
Hangover subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2	
Injection site inflammation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Injection site mass subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	
Seasonal allergy			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 0 / 9 (0.00%) 0	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dry throat subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	2 / 10 (20.00%) 2 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1	
Psychiatric disorders Libido decreased subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all) Mood altered subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Injury, poisoning and procedural complications			

Ligament sprain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	
Heat stroke subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Meniscus injury subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1	
Nervous system disorders Seizure subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 4	0 / 10 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3	1 / 10 (10.00%) 7	
Dizziness subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Sleep paralysis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 8	1 / 10 (10.00%) 3	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 4	1 / 10 (10.00%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4	0 / 10 (0.00%) 0	
Abdominal pain upper			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	3 / 9 (33.33%)	1 / 10 (10.00%)	
occurrences (all)	3	3	
Acne			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)	3 / 10 (30.00%)	
occurrences (all)	3	6	
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tinea versicolour			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Otitis media subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Subcutaneous abscess subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	
Appetite disorder subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2021	Protocol Version 2.0 changes: • Corrected duration of follow-up period from 4-week follow-up period to 3-week follow-up period based on change in Schedule of Assessments • Changed QD PK sampling to the first day of the run-in period instead of at the end of the Run-in period • 2.5 mg QD/25 mg QW dose levels were included in methodology, synopsis, diagnosis and main criteria for inclusion, investigational product, dosage, and mode of administration • Corrected duration of study based on change in the follow-up period to 30 weeks • Added clarity/specificity to endpoints • Corrected an error, i.e., 50% effective concentration=0.27 nM • Specified formula to calculate eGFR • Added PHQ-9 score of ≥ 15 during screening for depression • Added ability for patients to get re-screened once if the screen failure is due to an entry criterion result that may change over time • Added text on drug accountability, reconciliation, and record maintenance • Added a section and explained unblinding • Added details for measuring height and weight • Added clarification around administration of patient-reported and caregiver-reported Hunger and Hyperphagia questionnaires • Added optional activity sensor sub-study • To ensure better safety of patients, the outpatient measurements of vital signs were to be re-checked either by the patient's primary care physician or at the investigative site • Added specificity to distinguish injection sites for QW formulation from those with the QD formulation • Added general text about monitoring for depression and suicidality • Added clarification on baseline/screening version of the C-SSRS scale • Added PHQ-9 to monitor for depression • Added specificity to analysis in terms of change and percentage change from baseline to Week 14 • Added clarification of region measurement, length, and width as appropriate during in-clinical visits and if possible during telehealth visits
21 March 2022	Protocol Version 3.0 changes: • Revised study objectives and endpoints to capture PK profile and adjusted PK sample collection timepoints to better capture both QD and QW PK profiles • Moved efficacy endpoint to exploratory endpoints and expanded exploratory endpoints to yield additional supportive information • Statistical analyses were updated to reflect revised objectives and endpoints • Included an option for possible blinded interim analyses • Modified procedures for telehealth visits • Clarified language around re-screening criteria • Included additional guidance on conduct for the optional sub-study

07 July 2022	Protocol Version 4.0 changes: • Included language to require re-consent of patients who reach the age of consent during the study (as applicable) • Removed optional activity sensor sub-study • Provided flexibility for the Investigator to prioritize sampling for patients <18 years of age to minimize excessive venipunctures; included this flexibility for all assessments for patients <18 years of age • Widened predose PK sampling window to within 30 minutes of dosing; widened certain post dose PK sampling windows to ± 30 minutes • Provided clarity around PK sampling timepoints to ensure characterization of PK profile for QD and QW • Included new indication for setmelanotide (currently in US) • Included criteria for determining study termination and re-organized content flow in Section 5.0 • Broadened exclusion criterion #9 to include hypersensitivity to active investigational product • Revised exclusion criteria #12 and #13 to include patients who are either legally protected or patients who are related to anyone responsible for the conduct of the study • Aligned language to reflect intent of voluntary study participation • Amended language to describe criteria for study and/or site closure (Germany)
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported