Clinical trial results:
Long Term Extension Trial of setmelanotide (RM-493) for patients who have completed a trial of Setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway.

This extension trial was conducted to characterise the safety and tolerability of setmelanotide for up to 7 additional years in patients who had completed treatment in a previous setmelanotide study. Participants had obesity associated with genetic defects upstream of the melanocortin-4 (MC4) receptor in the leptin-melanocortin pathway or with obesity related to other abnormalities in the melanocortin-4 receptor (MC4R) pathway. Patients continued taking the same dose of setmelanotide that was being administered at completion of the index study or for patients receiving blinded study drug in the index study, the starting dose and titration schedule from the index study were used in this study. Dose level changes were allowed at any time based on safety or efficacy findings. Safety was the primary endpoint. There were no secondary endpoints.

Patients aged 2 or older as per local regulations could be enrolled in the study if they had completed participation in a previous setmelanotide clinical study.

Overall, 205 patients aged 6-68 years (median 17.0) entered the trial; 61% of patients were female.

The median duration of exposure, including time in the index trial, was 3.19 years (range: 0.3-7.6) and >50% of patients were treated for >3 years (including 10.7% treated for >=5years).

Summary

EudraCT number	2017-005006-35
Trial protocol	DE FR NL GB BE ES GR
Global end of trial date	09 January 2025
Results information	
Result version number	v1 (current)
This version publication date	18 July 2025
First version publication date	18 July 2025

Trial information

Trial identification

Sponsor protocol code	RM-493-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03651765
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)	EMEA-002209-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2025
Global end of trial reached?	Yes
Global end of trial date	09 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize safety and tolerability of setmelanotide in patients who had completed treatment in a previous trial with setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway and obesity related to other abnormalities in MC4R pathway.

Protection of trial subjects:

The study was conducted in accordance with the International Council for Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate 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 was in compliance with ICH-GCP and all applicable regulatory requirements.
Monitoring and auditing procedures developed or reviewed and approved by Rhythm were followed, in compliance with GCP guidelines.
To be eligible for continued treatment after 1 year on setmelanotide (including time on setmelanotide during the index study) patients had to display evidence of meaningful clinical benefit via weight-related treatment effect or other assessments. Thereafter, continued eligibility was assessed every 3 months.

Background therapy:

Female patients were allowed to use hormonal contraception as well as hormone replacement therapy. Unless concomitant medications were likely to present strong potential safety concerns, the goal of this protocol was to allow as many potential patients with these ultra-rare conditions as possible to participate in the study. Patients who entered this study could continue all current medications as prescribed. 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. If any new medication for weight loss or a glucagon-like peptide-1 (GLP-1) agonist was started prior to or during the extension study, the Sponsor was to be informed.

Evidence for comparator:

Not applicable; there was no comparator drug in this open-label extension trial.

Actual start date of recruitment	03 July 2018
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: 14
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Réunion: 4
Country: Number of subjects enrolled	United States: 102
Worldwide total number of subjects	205
EEA total number of subjects	74

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)	38
Adolescents (12-17 years)	68
Adults (18-64 years)	97
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged 2 or older as per local regulations could be enrolled in the study if they had completed participation in a previous setmelanotide clinical study.

Pre-assignment

Screening details:

All patients had completed participation in a previous setmelanotide clinical study.

Period 1

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

Blinding implementation details:

Not applicable; this was an open-label extension trial.

Arms

Arm title	Setmelanotide

Arm description:

This trial included patients from 7 index (parent) trials:
RM-493-011: N = 9
RM-493-012: N = 13
RM-493-014: N = 119
RM-493-015: N = 12
RM-493-023: N = 37
RM-493-030: N = 14
RM-493-034: N = 1

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

Dosage and administration details:

Patients received open label setmelanotide by subcutaneous (SC) injection QD each morning. Patients and/or their caretakers were responsible for all procedures associated with study drug administration throughout the study (i.e., drawing up, and administering study drug QD). Patients were instructed to rotate injection sites and to avoid tight fitting clothing near the injection site.
Patients began treatment at the same dose that was administered at the end of the index study, unless safety reasons justified a decrease, or if a potential effect on hunger or weight loss justified an increase. Setmelanotide doses >3 mg (or >5 mg in Germany, Canada, and the UK) were not permitted.
Patients previously on placebo began treatment using the local prescribing information up to a maximum dose based on the patient’s age and weight or the scheme used in the index study.

Number of subjects in period 1	Setmelanotide
Started	205
Completed	89
Not completed	116
Physician decision	6
Consent withdrawn by subject	24
Adverse event, non-fatal	6
Noncompliance with trial drug	4
Trial stopped by sponsor	40
Not specified	6
Pregnancy	1
Lost to follow-up	5
Withdrawal by parent/guardian	6
Lack of efficacy	18

Baseline characteristics

Reporting groups	
Reporting group title	Setmelanotide
Reporting group description:	
This trial included patients from 7 index (parent) trials: RM-493-011: N = 9 RM-493-012: N = 13 RM-493-014: N = 119 RM-493-015: N = 12 RM-493-023: N = 37 RM-493-030: N = 14 RM-493-034: N = 1	

Reporting group values	Setmelanotide	Total	
Number of subjects	205	205	
Age categorical Units: Subjects			
Children (2-11 years)	38	38	
Adolescents (12-17 years)	68	68	
Adults (18-64 years)	97	97	
From 65-84 years	2	2	
Age continuous Units: years			
median	17.0		
full range (min-max)	6 to 68	-	
Gender categorical Units: Subjects			
Female	125	125	
Male	80	80	

End points

End points reporting groups

Reporting group title	Setmelanotide

Reporting group description:

This trial included patients from 7 index (parent) trials:
RM-493-011: N = 9
RM-493-012: N = 13
RM-493-014: N = 119
RM-493-015: N = 12
RM-493-023: N = 37
RM-493-030: N = 14
RM-493-034: N = 1

Primary: Treatment-emergent adverse events

End point title	Treatment-emergent adverse events[1]

End point description:

The primary endpoint was the safety and tolerability of setmelanotide as assessed by the frequency of treatment-emergent adverse events (TEAEs).

End point type	Primary

End point timeframe:

Throughout the study from Visit 1 through the patient's last visit.

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 long-term extension trial to characterise safety and tolerability. Only a descriptive analysis of adverse events was planned.

End point values	Setmelanotide			
Subject group type	Reporting group			
Number of subjects analysed	205			
Units: Subjects				
At least 1 TEAE	198			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All AEs reported from a patient's first visit to their last visit in the trial were documented.	
Adverse event reporting additional description:	
Treatment-emergent AEs are displayed.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Setmelanotide

Reporting group description:

This trial included patients from 7 index (parent) trials:
RM-493-011: N = 9
RM-493-012: N = 13
RM-493-014: N = 119
RM-493-015: N = 12
RM-493-023: N = 37
RM-493-030: N = 14
RM-493-034: N = 1

Serious adverse events	Setmelanotide		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 205 (13.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer stage I			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Prostate cancer			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal neoplasm			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			

subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 205 (0.98%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hallucination, auditory			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obsessive-compulsive disorder			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 205 (0.98%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle spasticity			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Deafness unilateral			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			

subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	3 / 205 (1.46%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis Escherichia coli			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal disease			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Setmelanotide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 205 (96.59%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 205 (6.34%)		
occurrences (all)	13		
Blood creatine phosphokinase increased			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	12		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	41 / 205 (20.00%)		
occurrences (all)	62		
Injury, poisoning and procedural complications			
Immunisation reaction			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	23		
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	13		
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 205 (29.27%)		
occurrences (all)	114		
Dizziness			
subjects affected / exposed	16 / 205 (7.80%)		
occurrences (all)	19		
General disorders and administration site conditions			

Injection site erythema			
subjects affected / exposed	43 / 205 (20.98%)		
occurrences (all)	53		
Injection site induration			
subjects affected / exposed	35 / 205 (17.07%)		
occurrences (all)	41		
Injection site pruritus			
subjects affected / exposed	38 / 205 (18.54%)		
occurrences (all)	40		
Fatigue			
subjects affected / exposed	22 / 205 (10.73%)		
occurrences (all)	33		
Injection site pain			
subjects affected / exposed	26 / 205 (12.68%)		
occurrences (all)	31		
Injection site bruising			
subjects affected / exposed	25 / 205 (12.20%)		
occurrences (all)	25		
Pyrexia			
subjects affected / exposed	15 / 205 (7.32%)		
occurrences (all)	17		
Injection site haemorrhage			
subjects affected / exposed	12 / 205 (5.85%)		
occurrences (all)	12		
Injection site oedema			
subjects affected / exposed	16 / 205 (7.80%)		
occurrences (all)	17		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	28 / 205 (13.66%)		
occurrences (all)	43		
Abdominal pain upper			
subjects affected / exposed	20 / 205 (9.76%)		
occurrences (all)	31		
Vomiting			

subjects affected / exposed	21 / 205 (10.24%)		
occurrences (all)	29		
Diarrhoea			
subjects affected / exposed	17 / 205 (8.29%)		
occurrences (all)	25		
Abdominal pain			
subjects affected / exposed	20 / 205 (9.76%)		
occurrences (all)	24		
Tongue pigmentation			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	13 / 205 (6.34%)		
occurrences (all)	23		
Cough			
subjects affected / exposed	12 / 205 (5.85%)		
occurrences (all)	21		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	110 / 205 (53.66%)		
occurrences (all)	244		
Acne			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	12		
Eczema			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 205 (9.76%)		
occurrences (all)	30		
Pain in extremity			
subjects affected / exposed	16 / 205 (7.80%)		
occurrences (all)	23		
Back pain			

subjects affected / exposed	20 / 205 (9.76%)		
occurrences (all)	21		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 205 (15.61%)		
occurrences (all)	94		
Upper respiratory tract infection			
subjects affected / exposed	36 / 205 (17.56%)		
occurrences (all)	74		
Covid-19			
subjects affected / exposed	60 / 205 (29.27%)		
occurrences (all)	70		
Influenza			
subjects affected / exposed	22 / 205 (10.73%)		
occurrences (all)	27		
Urinary tract infection			
subjects affected / exposed	17 / 205 (8.29%)		
occurrences (all)	25		
Gastroenteritis			
subjects affected / exposed	15 / 205 (7.32%)		
occurrences (all)	18		
Ear infection			
subjects affected / exposed	12 / 205 (5.85%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2018	Clarified that there was to be no gaps of setmelanotide treatment during the transition from the index study to the extension study. Clarified that the participants must have demonstrated adequate efficacy as well as adequate safety in a previous setmelanotide study. Added language to indicate different maximum allowable doses across various countries depending on requirements of competent authorities. Decreased the maximum duration of patient participation from up to 5 years to up to 2 years.
15 October 2018	Entry criteria were updated to remove the requirement that a patient had to have shown efficacy in an index study to be eligible; patients had only to have completed participation in an index study and demonstrate safety in order to be eligible to enrol.
16 October 2019	Extended the study duration from 2 to 5 years Increased the expected number of patients from 100 to 150 Entry criterion was updated to include the requirement that a patient had to have shown clinical benefit (efficacy) in the index study in the opinion of primary investigator. Specified that the primary investigator could assess depression and suicidality in patients who were unable to complete PHQ-9 or C-SSRS questionnaires due to significant neurocognitive defect for the purpose of determining study exclusion criteria. Directions on dose adjustments were revised based on currently approved maximum daily setmelanotide dose in participating countries as well as current study drug administration guidance.
05 August 2021	Patients currently enrolled in this current study could exit the study at any time to participate in other setmelanotide clinical studies with the patients' written informed consent, at the discretion of the Investigator and Sponsor. The minimum age of enrollment was lowered from 6 to 2 years. Patients were required to have experienced meaningful clinical benefit during prior setmelanotide treatment, with meaningful benefits described.
09 November 2022	Clarified the patient population applied to patients with rare genetic, syndromic, or acquired diseases of obesity and obesity potentially related to other abnormalities in the MC4R pathway; included newly revised label indications for setmelanotide. Revised expected patient enrollment to 300 patients. Patients experiencing improvements in weight-related parameters or other meaningful clinical benefit would be further considered for study enrollment. Allowed for inclusion of patients who may clinically benefit from study participation at the discretion of the Investigator. Clarified that extension study re-entry would not be permitted if setmelanotide became commercially available for a given patient's condition. Added new information on dose adjustments based on BMI/BMI Z parameters and dosing considerations from other studies and provided further instruction for study drug administration.

12 May 2023	Permitted dose escalation up to 5 mg for adult patients who might benefit and had tolerated lower doses; provided rationale for dosing up to 5 mg and included reference to the IB for specific nonclinical and clinical experience. The total study duration was extended from 5 to 7 years; expanded potential number of patients up to 500. Provided clarity on initial starting dose and titration steps for patients who enter from a double-blind index study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This was a long-term extension trial with a heterogenous population of patients, all treated with open-label setmelanotide. Safety was the primary endpoint. There were no secondary endpoints.

Notes: