A 2-Stage (Open-Label Followed by Randomized Double-Blind, Placebo-Controlled Stage), Phase 2 Trial of Setmelanotide in Patients with Specific Gene Variants in the Melanocortin-4 Receptor Pathway

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Primary:• To evaluate the proportion of patients with obesity with genetic variants in a specific gene in the melanocortin-4 receptor (MC4R) pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide at the end...

Ethical review	Approved WMO
Status	Completed
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54472

Source
ToetsingOnline

Brief title
RM-493-034

Condition

- Metabolic and nutritional disorders congenital

Synonym
Gene defects, obesity

Research involving

Human

Sponsors and support

Primary sponsor: Rhythm Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Rhythm Pharmaceuticals

Intervention

Keyword: genetic defects, Obesity

Outcome measures

Primary outcome

• The proportion of patients by genotype who demonstrate a significant

clinically meaningful response (defined below) to setmelanotide at the end of

Stage 1:

* For all patients: achieving a >=5% reduction in BMI from Baseline

Secondary outcome

Secondary:

• Mean change and percent change in BMI from Baseline to end of Stage 1 in all

patients and patients >=18 years old, per gene

• Mean change and percent change in body weight from Baseline to end of Stage 1

in patients >=18 years old, per gene

• Mean change in BMI Z-score from Baseline to end of Stage 1 in patients <18

years old, per gene

• Mean percent change in the weekly average of the daily maximal hunger score

from Baseline to end of Stage 1 in patients >=12 years old, per gene

• The proportion of patients >=12 years old, per gene, who achieve a >=2-point

reduction (improvement) from Baseline to end of Stage 1 in the weekly average

of the daily maximal hunger score.

Exploratory:

• Mean change from Baseline to end of Stage 1 in total score for the 5-level EuroQol 5 Dimension questionnaire (EQ-5D-5L in patients >=16 years old and EQ-5D-5L Proxy version in patients <16 years old), per gene, at the end of open-label treatment

• Mean change from Baseline to end of Stage 1 in physical functioning score and total score for the Impact of Weight on Quality of Life (IWQOL) (IWQOL-Lite in patients >=18 years old and IWQOL-Kids in patients 11- <18 years old), per gene, at the end of open-label treatment

• Mean change in waist circumference from Baseline to end of Stage 1 in patients >=12 years old, per gene

• Mean change from Baseline to the end of Stage 2, per gene, in metabolic parameters including: fasting glucose, HbA1C, lipid profiles (total-, high-density lipoprotein [HDL]-, and low-density lipoprotein [LDL]-cholesterol, triglycerides) in patients in the setmelanotide arm compared to placebo arm

• Mean change from Baseline to the end of Stage 1 per gene, in metabolic parameters including: fasting glucose, HbA1C, lipid profiles (total-, HDL-, and LDL-cholesterol, triglycerides)

• Proportion of setmelanotide-treated patients by genotype who achieve a >=5% reduction in BMI from Baseline at the end of Stage 2 compared to placebo

• Mean change and percent change in BMI from Baseline to end of Stage 2 in all patients and patients >=18 years old, per gene, for the setmelanotide group

compared with the placebo group

• Mean change and percent change in body weight from Baseline to end of Stage 2 in patients >=18 years old, per gene, for the setmelanotide group compared with the placebo group

• Mean change in BMI Z-score from Baseline to end of Stage 2 in patients <18 years old, per gene, compared with the placebo group

• Mean change in waist circumference from Baseline to end of Stage 2 in patients >=12 years old, per gene

• Mean percent change in the weekly average of the daily maximal hunger score from Baseline to end of Stage 1 in patients >=12 years old, per gene

• The proportion of patients >=12 years old, per gene, who achieve a >=2-point reduction (improvement) from Baseline to end of Stage 2 in the weekly average of the daily maximal hunger score for the setmelanotide group compared with the placebo group

• Mean change from Baseline to end of Stage 2 in total score for the (EQ-5D-5L in patients >=16 years old and EQ-5D-5L Proxy version in patients <16 years old) in the setmelanotide arm compared to the placebo group, per gene

• Mean change from Baseline to end of Stage 2 in physical functioning score and total score for the IWQOL (IWQOL-Lite in patients >=18 years old and IWQOL-Kids in patients 11- <18 years old), per gene

• Mean change from Baseline to end of Stage 2 in the Symptoms of Hyperphagia questionnaire (Patient version in patients >=12 years old and Caregiver version in patients 6 to <12 years old), per gene, in the setmelanotide arm compared to the placebo arm

• Safety and tolerability assessed by the frequency and severity of AEs,

changes in vital signs, and changes in laboratory evaluations at the end of

Stage 1 and Stage 2.

Study description

Background summary

The melanocortin-4 receptor (MC4R) pathway is the principal regulator of mammalian energy balance and body weight. Originating in the hypothalamus it concertedly modulates appetite (feelings of hunger and satiety), energy intake (as caloric consumption), and energy expenditure (basal metabolism, thermogenesis, and physical activity) to define long term body weight. In humans and animal models, genetic defects in this pathway result in severe forms of early-onset obesity and unrelenting hunger (Farooqi 2008). Mechanistically these forms of obesity arise due insufficient activation of MC4Rs leading to overconsumption of food and a reduction in energy utilization. Setmelanotide, a MC4R agonist, has the potential to restore reduced activity in MC4Rs in patients with these genetic defects in MC4R pathway. Thus, setmelanotide may serve as a form of *replacement* therapy to re-establish weight and appetite control in patients with these disorders.

Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a potent MC4R agonist. Setmelanotide binds with high affinity (inhibitory constant = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration = 0.27 nM). While not an analog, it retains the specificity and functionality of the naturally occurring pro-opiomelanocortin (POMC)-derived neuropeptide, alpha-melanocyte-stimulating hormone (α-MSH), which is the endogenous ligand for the MC4R. Setmelanotide is more potent and has a much longer half-life (~10-12 hours in humans) than the short-lived α-MSH ligand.
The setmelanotide peptide was initially selected for clinical development based on its acceptable circulating half-life as a saline formulation (2.8-3.5 hours in nonhuman primates) and the ability to decrease body weight gain and suppress food intake in normal rats. Preclinical studies demonstrated the efficacy of setmelanotide in suppressing food intake and body weight gain in diet-induced obese mice, rats, dogs, and monkeys, as well as in genetic models of obesity, including leptin-deficient ob/ob mice and leptin receptor deficient obese Zucker rats. Later studies in obese monkeys showed that setmelanotide did not increase blood pressure (BP) or heart rate (HR), a potential concern observed with other MC4R agonist compounds.

By restoring impaired signaling in the MC4R pathway, setmelanotide can serve as an indirect form of replacement therapy for patients with genetic defects that lead to extreme obesity, with the potential for dramatic improvements in body weight and appetite control.

Study objective

Primary:
• To evaluate the proportion of patients with obesity with genetic variants in a specific gene in the melanocortin-4 receptor (MC4R) pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide at the end of open-label treatment

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

Exploratory:
• To evaluate change in quality of life and waist circumference in response to setmelanotide in patients with genetic variants in a specific gene in the MC4R pathway at the end of open-label treatment
• To evaluate the change in metabolic parameters in response to treatment with setmelanotide at the end of Stage 1 and at the end of Stage 2
• To evaluate the proportion of patients with obesity with genetic variants in a specific gene in the MC4R pathway who achieve a clinically meaningful reduction in body weight in response to setmelanotide at the end of the Stage 2 compared to placebo
• To evaluate change in weight parameters, waist circumference, hunger and quality of life in response to setmelanotide in patients with genetic variants in the MC4R pathway at the end of the Stage 2 compared to placebo

Safety:
• To evaluate the safety and tolerability of setmelanotide in patients with genetic variants in the MC4R pathway

Study design

A 2-Stage (Open-Label Followed by Randomized Double-Blind, Placebo-Controlled Stage), Phase 2 Trial. Participation may last for up to 1 year (52 weeks). This study has 4 main periods:
-Screening period (up to 8 weeks)
- The treatment:
o Open-label treatment period (up to 16 weeks)
o Double-blind treatment period (up to 24 weeks)
- Follow- up period (4 weeks)

Intervention

A 2-Stage (Open-Label Followed by Randomized Double-Blind, Placebo-Controlled Stage), Phase 2 Trial.
In stage 1 of the study, the patient injects setmelanotide daily for 16 weeks.
In stage 2 of the study, all patients will be randomized 2:1 to receive continuous daily administration of setmelanotide or matching placebo (24 weeks).

During the blinded treatment period the study doctor will monitor patient's weight. Depending on patient's weight, patient may be offered to start treatment with the study drug through a long-term extension (LTE) study. This is a separate study. If this LTE study is not yet available at the study center, patient may be able to receive the study drug until the LTE study is available (through bridging visists).

Study burden and risks

The following side effects have been reported in patient who took setmelanotide (approximately 10% or more patients):
• Skin darkening or discoloration
• Nausea
• Headache
• Vomiting
• Injection site reactions as such as pain, itching, redness, or skin hardening
• Increased intermittent/spontaneous penile erections (in male patients)
• Diarrhea
• Tiredness

Discomforts: Penile erections in males; Discomfort in females; Benzyl Alcohol Risk;
Allergic Reaction Risk

The following side effects are considered common and have been reported by patients who took setmelanotide (at least 2% but less than 10% of patients):
• Decreased appetite
• Pain in the back, joint pain or stiffness or muscle aches or pain
• Injection site reactions such as swelling, bruising, discoloration, fluid retention, bleeding
• Infection in the upper air way, or common cold symptoms, nasal congestion, throat pain
• Freckles
• Dry skin or mouth
• Insomnia
• Dizziness
• Abdomen pain, indigestions (dyspepsia) or gastric reflux
• Constipation

• Disturbances in sexual arousal
• Itching and rash
• Flu, stomach flu and flu-like symptoms
• DepressionIncrease in sexual interest
• Lack of energy
• Painful menstrual cramps (in female patients)
• Fever
• Cough
• Urinary tract infection
• Anxiety
• High blood pressure
• Increased liver lab values (ALT)
• Increased blood enzyme lab values (CPK)
• Low red blood cell count (anemia)

Contacts

Public
Rhythm Pharmaceuticals, Inc.

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Scientific
Rhythm Pharmaceuticals, Inc.

Berkeley Street 222
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)

Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

1. Patients must have a pre-identified genetic variant in an established MC4R pathway gene that contributes to obesity
Note: Genetic testing requirements and a list of genes which have variants that are eligible for enrollment into the trial are provided in Appendix 1 of the protocol.
2. Patients between the ages of 6 and 65, inclusive, at the time of signing Informed Consent or Assent.
3. Patients with obesity, defined as BMI >=40 kg/m2 for patients >=18 years of age or BMI >=97th percentile for age and gender for patients 6 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
4. Patient and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the trial (including the QD injection regimen and all other trial procedures) and is able to understand and sign the written informed consent/assent. Patients who are unable to comply with all trial procedures due to cognitive limitations or any other reason should not be enrolled.
5. Patient must meet one of the following requirements:
Female participants of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must be confirmed non-pregnant and agree to use a highly effective form of contraception throughout the trial and for 90 days following the trial.
Highly effective forms of contraception are detailed below and in Section 8.9.7 of the protocol:
• Combined (estrogen and progestin) hormonal contraception associated with inhibition of ovulation (i.e., oral, intravaginal, or transdermal)
• Progestin-only hormonal contraception associated with inhibition of ovulation (oral, implantable, or injectable)
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomy/vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the female participant, and the vasectomized partner has received medical assessment of surgical success)
• Sexual abstinence, only if it is the preferred and usual lifestyle of the patient
Female participants of non-childbearing potential, defined as: permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or post-menopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone level in the post-menopausal lab range)

and do not require contraception during the trial.
Younger female patients who have not achieved sexual maturity at trial entry will be assessed for Tanner staging and required to comply with contraception requirements at first menarche.
Male participants with female partners of childbearing potential must agree to use a highly effective method contraception if they become sexually active during the trial or within 90 days following their participation in the trial.
Male patients must also not donate sperm during and for 90 days following their participation in the trial.
6. Symptoms or behaviors of hyperphagia persistent during the patient*s life, including manifestations in childhood, as determined by the Investigator at screening.

Exclusion criteria

1. Patients with the following genetic variants: biallelic Bardet-Biedl Syndrome (BBS); biallelic Alström Syndrome 1 (ALMS1); homozygous, heterozygous, or compound heterozygous variants in MC4R, POMC, PCSK1, LEPR, nuclear receptor coactivator 1 (NCOA1; steroid receptor coactivator-1 [SRC1]) or SRC homology 2 B adapter protein 1 (SH2B1) genes as well as 16p11.2 chromosomal deletions that include the SH2B1 gene.
2. Weight loss >2% in the previous 3 months.
Patients will not be excluded for using regimens for weight maintenance or to prevent weight gain, such as dietary and/or exercise regimens, or medications, supplements or herbal treatments (e.g., orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc.), provided:
• the regimen and/or dose has been stable for at least 3 months prior to randomization
• the patient has not experienced weight loss >2% during the previous 3 months, AND
• the patient intends to keep the regimen and/or dose stable throughout the course of the trial.
3. Bariatric surgery or procedure (e.g., gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc.) within the last 6 months.
All patients with a history of bariatric surgery or procedures must be discussed with, and receive approval from, the Sponsor prior to enrollment.
4. Documented diagnosis of current unstable major psychiatric disorder(s) (e.g., major depressive disorder, bipolar disorder, schizophrenia, etc.) or documented worsening psychiatric condition that required changes in treatment regimen within the previous 2 years, or other psychiatric related risks that the Investigator believes may interfere with trial compliance or patient safety.
5. Clinically significant depression or suicidality, as defined by: any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) during Screening, any suicide attempt during the patient*s lifetime,

any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of >=15 during Screening process.
Note: Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive impairment may be enrolled in the trial provided that there are no clinical signs or symptoms of significant depression or suicidal behavior in the opinion of the Investigator.
6. Current, clinically significant pulmonary, cardiac, endocrine/metabolic, hepatic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. Significant features of, or meeting the diagnostic criteria for, a genetic syndrome that is associated with obesity.
Note: Although some of the genetic variants that are eligible to be enrolled into this trial are associated with specific syndromes, the intent of this trial is not to enroll children with significant cognitive impairment or other significant co-morbidities. Patients with eligible genetic variants, but who otherwise do not exhibit the syndrome, are eligible for enrollment.
8. HbA1C >10.0% at Screening.
9. History of significant liver disease other than non-alcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Patients with NAFLD or NASH will not be excluded based on this criterion
10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 at Screening. In patients >18 years of age the Modification of Diet in Renal Disease (MDRD) Equation should be used to calculate eGFR. In patients <18 years of age, the Bedside Schwartz Equation should be used for calculation of GFR.
11. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
Note: If the type of skin cancer in patient*s or close family history is not known, then the patient should not be enrolled into the trial.
12. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of concern, the patient may need to be excluded from the trial.
13. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
14. Participation in any clinical trial with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first day of dosing.
15. Patients previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
16. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).

17. Females who are pregnant or breastfeeding or planning or desiring to become pregnant during the duration of the trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-10-2022
Enrollment:	11
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Setmelanotide
Generic name:	Setmelanotide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-11-2021
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-05-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	21-11-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-002855-12-NL
CCMO	NL79380.078.21