Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with rare genetic disorders of obesity

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Main objective:To explore the impact of setmelanotide on obesity in patients with various specific rare genetic mutations.Secondary objective:To assess the effects of setmelanotide on:* Safety and tolerability-Hunger* Waist circumferenceOptional sub...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Appetite and general nutritional disorders
Study type	Interventional

Summary

ID

NL-OMON49642

Source
ToetsingOnline

Brief title
Setmelanotide (RM-493) Phase 2 Treatment Trial in Patients with obesity

Condition

- Appetite and general nutritional disorders

Synonym
genetic mutation, Obesity

Research involving
Human

Sponsors and support

Primary sponsor: RHYTHM Pharmaceuticals
Source(s) of monetary or material Support: RHTYHM Pharmaceutical Inc.

Intervention

Keyword: Genetic defect (MC4- Receptor) agonist, Obesity, setmelanotide (RM-493)

Outcome measures

Primary outcome

The proportion of patients in each subgroup of RGDO who achieve at least 5%

body weight reduction from baseline, at ~3 months treatment with setmelanotide.

Measured At the end of ~3 months of treatment.

Secondary outcome

Secondary endpoints:

* Safety and tolerability of setmelanotide injection, assessed by the frequency

and severity of AEs, vital signs, and laboratory evaluations

* Change and percentage change from baseline in body weight

* Change from baseline in Daily and Global Hunger scores

* Change from baseline in waist circumference

Exploratory Endpoints

* Change from baseline in total body mass, including body fat and non-bone lean

mass, as measure by either dual-energy x-ray

absorptiometry (DXA) or bioelectrical impedance (BIA)

* Change from baseline in fasting lipids (total cholesterol, high density

lipoprotein cholesterol, low density lipoprotein cholesterol, and

triglycerides)

* Change from baseline in metabolic and hormonal assays and other exploratory biomarkers

* Change from baseline in glycated hemoglobin (HbA1c)

* Evaluation of plasma pharmacokinetic (PK) parameters

* Change from baseline in quality of life as measured by the following assessments:

* Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

* EuroQoL-Five Dimension-5L (EQ-5D-5L) or EuroQoL-Five Dimension-Y (EQ-5D-Y)

* The 12-Item Short Form Health Survey (SF-12) or 10-Item Short Form Health Survey for Children (SF-10)

* Patient-Reported Behavioral Disturbance Questionnaire

* Change from baseline in mental health status as measured by the Patient Health Questionnaire-9 (PHQ-9) and Columbia-Suicide Severity Rating Scale (C-SSRS)

* Tanner Staging for patients who have yet to reach Tanner Stage V

Study description

Background summary

Rhythm Pharmaceuticals, Inc. has developed the trial drug setmelanotide, a MSH messenger substance, to replace the messenger substances that are missing in someone with certain gene variations.

The objective of this study is to demonstrate clinically meaningful weight loss in patients with various rare genetic forms of obesity after a stable

therapeutic dose period, which is expected to be ~3 months of treatment in most subjects. The primary endpoint is defined as the proportion of patients in each subgroup of rare genetic disorders of obesity (RGDO) who achieve at least 5% body weight reduction from baseline, at ~3 months of treatment with setmelanotide.
The study is exploratory in nature and the sample size of the study for each cohort is driven by clinical considerations. The total number of patients enrolled per subtype with specific genetic obesity mutations may be increased or decreased, depending upon the total number of affected patients identified. These many rare genetic disorders are grouped together into one protocol for administrative reasons, and otherwise would have been studied in separate protocols. Hence, each rare genetic disorder will be treated as a separate population for any statistical analysis, and therefore no multiplicity adjustments will be planned in this early, proof-of-concept study.

The drug is administered once a day by subcutaneous injection (under the skin).
The dosage is an once daily dosing; for patients 6 up to 16 years of age, 1.0, 2.0, or 3.0 mg, and for patients *16 years of age, 2.0 or 3.0 mg

All patients receive study treatment for 16 weeks. Patients may elect to continue setmelanotide treatment by enrolling in an extension study (RM-493-022) immediately following the last dose in this study; if the extension study is not yet open at the current clinic site, patients may continue treatment in the current study for up to one year, resulting in treatment duration of up to 16 months.

Criteria for evaluation:
Efficacy:

The primary efficacy endpoint is the percent of patients in each subgroup showing at least a 5% loss of body weight over ~3 months. Therefore, monthly weight measurements will be obtained throughout the course of the trial. Supporting efficacy endpoints will include change from baseline in Daily and Global Hunger scores, body composition assessments (including total body weight, fat mass, and non-bone lean mass) and waist circumference.
Safety:

The safety and tolerability of setmelanotide once daily (QD) subcutaneous (SC) injection will be assessed by the frequency and severity of adverse events (AEs) as well as changes in vital signs and laboratory evaluations.
Potential improvements in lipids (fasting cholesterol and triglycerides) as well as glucose parameters as measured by fasting glucose and glycated hemoglobin (HbA1c) will be assessed over time.
As required by Food and Drug Administration (FDA) for central nervous system (CNS)-active obesity medications, changes in depression/suicidality as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) and Patient Health

Questionnaire 9 (PHQ-9) will be monitored over the course of the trial.

Study objective

Main objective:

To explore the impact of setmelanotide on obesity in patients with various specific rare genetic mutations.

Secondary objective:

To assess the effects of setmelanotide on:
* Safety and tolerability
-Hunger
* Waist circumference

Optional sub-study to further evaluate the PK profile.

participating in the 24-hour sub-study, 4 additional blood samples will be collected after the same dose:
* 9, 10, and 12 hours (± 10 min) after dosing, and
*At approximately 24 hours after dosing; specifically, within 10 minutes BEFORE the next dose of study drug.

Study design

This is a Phase 2 open-label, uncontrolled, proof-of-concept study assessing the effect of setmelanotide on patients with rare genetic disorders of obesity for which evidence supports a role of the leptin-melanocortin hypothalamic pathway (the *MC4 pathway*). This study is designed as a *basket study*, using similar procedures to assess treatment effects on different genetic populations that share similar phenotypes of early onset, severe obesity and hyperphagia. The differing rare genetic causes of obesity that will be enrolled in this study are collectively referred to as different subgroups.

Intervention

Patient questionnaires
Blood sampling (safety, biomarkers, fasting Lipid panel, PK, Anti-RM-493 antibody)
Body composition (BIA, DXA)
Measurement Blood pressure, HR and ECG

Sub-study * if consented * PK sampling

Study burden and risks

Overall, setmelanotide has been generally well-tolerated in previous studies. Drug *Related Treatment Emerengy AE*s (for which the adverse event was assessed as possible or probably related to the study drug by the investigator) were reported.

RM-493 has been given to 334 patients in studies ranging from a single dose to a couple of years of treatment. It has been given to both healthy volunteers and people suffering for a variety of diseases. The studies were conducted to test the safety of RM-493 and, in some cases, to measure weight loss.

Pharmacodynamic data from a variety of animal models have shown improvements in weight regulation, appetite suppression and energy expenditure. Setmelanotide has also demonstrated meaningful weight reductions in early healthy obese volunteer clinical studies. In a Phase 2 proof-of concept study, three LEPR deficient patients were treated with setmelanotide and each demonstrated compelling improvements on weight loss and hunger, with no signs of increased blood pressure or heart rate.

The PI and staff (and other covering clinicians) will be available at all times to study participants in the event of a clinical emergency: both this availability and how to reach the investigator in an emergency will be clearly communicated orally and in writing to the study participants. All study interventions will be provided free of cost.
The current Investigator Brochure describes a comprehensive summary of AEs reported to date

Contacts

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RHYTHM Pharmaceuticals

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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)
Elderly (65 years and older)

Inclusion criteria

1. Patients with the following genotypes and/or clinical assessment:
a. POMC/PCSK1/LEPR heterozygous
b. POMC/PCSK1/LEPR compound heterozygous (two different mutations in gene) or homozygous deficiency obesity
c. POMC/PCSK1/LEPR composite heterozygous (two or more mutations in two or more genes) deficiency obesity
d. Smith-Magenis Syndrome (SMS)
e. SH2B1 deficiency obesity
f. Chromosomal rearrangement of the 16p11.2 locus causing obesity
g. CPE compound heterozygous or homozygous deficiency obesity
h. Leptin deficiency obesity with loss of response to metreleptin
i. SRC1 deficiency obesity
j. MC4R deficiency obesity
Note: The specific genotype for all patients must be reviewed by the Sponsor prior to study enrollment to confirm that the patient meets Inclusion Criterion #1. In addition, enrollment of patients in some subgroups may be prioritized by the Sponsor in order to ensure enrollment of patients with (1) well described, loss-of-function genetic mutations, (2) a variety of genetic variants, or (3) genetic variants likely to respond to setmelanotide.
2. Age 6 years and above.
3. Obese, defined as Body Mass Index (BMI) * 30 kg/m2 for patients *16 years of age or BMI * 95th percentile for age and gender for patients 6 up to 16 years of age.
4. Study participant and/or parent or guardian is able to communicate well with the Investigator, to understand and comply with the requirements of the study, and is able to understand and sign the written informed consent/assent.

5. Female participants of child-bearing potential must be confirmed non-pregnant, and agree to use contraception as outlined in the protocol. Female participants of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening Follicle-Stimulating Hormone [FSH] level in the post-menopausal lab range), and failure to have achieved menarche, do not require contraception during the study.
6. Male participants with female partners of childbearing potential must agree to a double-barrier method if they become sexually active during the study. Male patients must not donate sperm during and for 90 days following their participation in the study.

Exclusion criteria

1. Recent intensive (within 2 months) diet and/or exercise regimen with or without the use of weight loss agents including herbal medications that has resulted in > 2% weight loss.
2. Use of any medication that is approved to treat obesity within three months of first dose of study drug (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion). Note: Glucagon-like peptide-1 (GLP-1) receptor agonists may be used up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) is it not being prescribed for the treatment of obesity, (2) the dose has been stable for at least three months prior to enrollment, (3) the patient has not experienced weight loss during the previous three months, AND (4) the patient intends to keep the dose stable throughout the course of the study.
3. Gastric bypass surgery within the previous six months or any prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain. Specifically, patients may be considered if surgery was not successful, or resulted in <10% weight loss compared to pre-operative baseline weight or clear evidence of weight regain after an initial response to bariatric surgery. All patients with a history of bariatric surgery must be discussed with and receive approval from the Sponsor prior to enrollment.
4. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other psychiatric disorder(s) that the Investigator believes will interfere significantly with study compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
5. A PHQ-9 score of * 15 or any suicidal ideation of type 4 or 5 on the C-SSRS during Screening, any lifetime history of a suicide attempt, or any suicidal behavior in the last month. Note: Patients who are unable to complete the PHQ-9 or C-SSRS due to significant neurocognitive defects may be allowed to enroll in the study, as long as in the opinion of the Primary Investigator there are no

clinical signs or symptoms of suicidal behavior.
6. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor to determine eligibility.
7. HbA1c >9.0% at Screening
8. History of significant liver disease or abnormal liver tests on Screening (i.e. > 1.5 x upper limit of normal [ULN] for alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin). Note: Patients entering the study with SRC1 haploinsufficiency obesity must be evaluated during the Screening Period for hepatic fibrosis by appropriate imaging techniques (e.g., transient elastography or magnetic resonance elastography). Any patient with moderate or greater fibrosis (e.g., the equivalent of a METAVIR score * 2) will be excluded from the study. Note: A patient with a diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) may be allowed to enroll in the study, after consultation with the Sponsor. Other significant liver disease, such as cirrhosis, are exclusionary.
9. Glomerular filtration rate (GFR) < 30 mL/min at Screening.
10. History or close family history (parents or siblings) of skin cancer or melanoma (not including non-invasive/infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
11. 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 a qualified dermatologist during Screening. Any concerning lesions identified during the Screening Period 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 study.
12. Patient is, in the opinion of the Study Investigator, not suitable to participate in the study.
13. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.
14. Patients previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
15. Significant hypersensitivity to any excipient in the study drug.
16. Inability to comply with QD injection regimen.
17. Females who are breastfeeding or nursing.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-06-2020
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Setmelanotide (RM-493)
Generic name:	Setmelanotide (RM-493)

Ethics review

Approved WMO Date:	21-08-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2022
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	EUCTR2017-000387-14-NL
ClinicalTrials.gov	NCT03013543
CCMO	NL70159.078.19