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

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To characterize safety and tolerability of setmelanotide in patients who have completed treatment in a previous trial of setmelanotide for obesityassociated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway and...

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

Summary

ID

NL-OMON54784

Source
ToetsingOnline

Brief title
Trial for who have completed a trial of RM-493 for treatment of 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. 222 Berkeley Street;Suite 1200 MA 02116 Boston USA

Intervention

Keyword: Genetic defect (MC4- Receptor), Long term Open label, Obesity, setmelanotide (RM-493)

Outcome measures

Primary outcome

To characterize safety and tolerability of setmelanotide in patients who have completed treatment in a previous trial of setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway.

Secondary outcome

Exploratory

• Mean percent change from baseline in body weight in patients >=18 years of age.

• Mean change from baseline in BMI Z-score and percent of 95th BMI percentile in patients <18 years of age.

• Mean change in BMI and mean percent change in BMI from baseline in all patients.

• Change in hunger from baseline, as assessed at each visit using a set of 2

global questions.

• Change from baseline in waist circumference, as measured by US National Heart Lung and Blood Institute criteria [2000 NHLBI] over time.

• Yearly change in body composition including total body weight loss, fat loss, and non-bone lean mass, as measured by DXA scan or BIA.

• Change from baseline in lipid values (e.g., fasting cholesterol and triglycerides)

Changes from baseline in Quality of life as assessed by following instruments:

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

o 10-Item Short Form Health Survey for Children (SF-10)

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

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

Study description

Background summary

A genetic modification has been identified on the genes that play a key role in the regulation of our body weight. Sometimes there is a genetic change (variation) in one of the genes which are important for body weight regulation. These genes are responsible for helping to control weight and hunger regulators located in the hypothalamic centre in the brain that controls appetite and weight. When there are variations in these genes, they do not function as they should and the messenger substances (Melanocyte stimulating hormone - MSH) which signal the feeling of being full are no longer produced. This can result in you not feeling full and cause you to eat too much and become overweight

Rhythm Pharmaceuticals, Inc. is developing the trial drug setmelanotide, a MSH messenger substance, to replace the messenger substances that are missing in someone with certain gene variations.
The drug is administered once a day by subcutaneous injection (under the skin). Patients will be taught how to give the injection to themselves, so the daily injections can be performed at home. There will also be home nurse who is able to assist with the injections at home if required.

Setmelanotide has been given to more than 476 people with obesity ranging from 1 dose to more than a year of dosing. It is only possible to tell what side effects these people have experienced. The studies were conducted to test the safety of setmelanotide and in some cases to measure weight loss.

An extension study is a research study designed to enable participants to continue receiving the study drug after the previous clinical study has end. This will be an open label extension study with setmelanotide.

Study objective

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

Study design

This is a long-term extension trial to study the safety and tolerability of continued setmelanotide treatment in patients who have completed a previous clinical trial on treatment with setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin.
Patients who complete treatment in a previous trial (index trial) of setmelanotide and wish to continue with setmelanotide treatment will be considered for eligibility to enter this extension study. Patients will be consented and eligibility confirmed prior to completion of their index trial.
Visit one of this trial will coincide with the final visit of the index trial.
There should be no gaps of setmelanotide treatment during transition from their index trial to this extension trial. Patients will begin this extension trial on the same dose of setmelanotide that they were taking when they complete their index trail. Patients will be evaluated every 3months at the study site for adverse events, concomitant meds, weight, waist circumference and hunger score.
Additional tests will be completed at longer study visit intervals.

Intervention

Patient questionnaires
Blood sampling (safety, Metabolic and Hormonal assays, PK and Anti-RM -493 antibody)
Body composition (BIA, DXA)

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) wer reported.
Because very few studies have been done using setmalanotide, there may be other unknown side effects.
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

Public
RHYTHM Pharmaceuticals

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Scientific
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)

Inclusion criteria

1. Patients aged 2 or older (or aged >2 years as per local regulations; only patients aged 12 years or older may be enrolled in the trial in Greece; only patients 6 years or older may be enrolled in the trial in Germany) who have completed participation in a previous setmelanotide clinical trial.

2. If patient received setmelanotide on an open-label basis in a previous setmelanotide clinical trial, patient demonstrated adequate safety and meaningful clinical benefit (efficacy) in the previous setmelanotide trial. Meaningful clinical benefit is defined as follows:
• Patients 18 years of age or younger that have completed participation on active drug and demonstrated adequate safety and at least 3% BMI reduction or reduction in BMI Z-score of 0.2 compared to baseline.
• Patients over 18 years of age should show reduction of 3% BMI compared to baseline. If the patient received trial drug in a double-blind basis in the previous placebo-controlled clinical trial, patient tolerated trial drug in the previous clinical trial.

3. Patient and/or parent or guardian is able to communicate well with the Principal Investigator, to understand and comply with the requirements of the trial, and to understand and sign the written informed consent/assent. The patient must assent/consent to participate in the trial.

4. Patient must meet one of the following requirements regarding contraception:
• If a female of childbearing potential, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), must use a highly effective form of contraception as outlined in Section 6.2.1.

• If a female 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 (FSH) level in the post-menopausal laboratory range), contraception is not required during the trial.
* Younger female patients who have not reached menarche upon trial entry will be assessed for Tanner staging and at first menarche will be required to comply with contraception requirements and pregnancy testing as outlined in the protocol.
• If a male with female partner(s) of childbearing potential, must agree to a double barrier method if they become sexually active during the study. Furthermore, male patients must not donate sperm during and for 90 days following their participation in the study.

Exclusion criteria

ALL Patients:
1. Pregnant and/or breastfeeding women
2. Significant dermatologic findings relating to melanoma or premelanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a screening comprehensive skin evaluation performed by a qualified dermatologist. 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 trial.
3. Patient is, in the opinion of the Study Investigator, not suitable to participate in the trial.
4. Current, clinically significant disease, if severe enough to interfere with the study and/or would confound the results. Any such patients should be discussed with the Sponsor prior to enrollment in the trial
5. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders (DSM-III) disorders that the investigator believes will interfere significantly with trial compliance.
6. A Patient Health Questionnaire-9 (PHQ-9) score of >= 15.
7. Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). 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 enrolled in the study, as long as in the opinion of the Primary Investigator there are no clinical signs or symptoms of suicidal behavior since the last visit in the index study.
8. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests (as indicated by abnormal liver function tests, alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, or serum bilirubin >1.5× the upper limit of 4 normal [ULN] for any

of these tests) for an etiology other than nonalcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed non-alcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not be exclusionary.
9. Severe renal dysfunction as defined by a glomerular filtration rate (GFR) <30 mL/min/1.73 m2 in patiënts >12 years of age.
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 ocularcutaneous albinism.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-09-2019
Enrollment:	14
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Setmelanotide (RM-493)
Generic name:	Setmelanotide (RM-493)

Ethics review

Approved WMO Date:	17-04-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2020
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:	04-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2021
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:	27-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2024
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	EUCTR2017-005006-35-NL
ClinicalTrials.gov	NCT03651765
CCMO	NL69205.078.19