An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset Leptin Receptor (LEPR) Deficiency Obesity due to Bi-Allelic Loss-of-Function LEPR Genetic mutations

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

Summary

ID

NL-OMON48914

Source
ToetsingOnline

Brief title
A 1-year of setmelanotide in patients with LEPR deficiency 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: RHYTHM pharmaceuticals

Intervention

Keyword: 1 year, LEPR deficiency, obesity, setmelanotide

Outcome measures

Primary outcome

To demonstrate statistically significant and clinically meaningful effects of

setmelanotide on percent body weight change in patients with LEPR deficiency

obesity due to rare bi-allelic or loss-of function mutations at the end of 1

year of treatment.

Secondary outcome

Secondary

To assess the effect of setmelanotide, over one year, on:

* Safety and tolerability of setmelanotide (including blood pressure [BP] and

heart rate [HR]).

* Hunger.

* Percent change in body fat mass.

* Glucose parameters: fasting glucose, glycated hemoglobin (HbA1c), oral

glucose tolerate test (OGTT) with focus on parameters of insulin sensitivity.

* Waist circumference.

* During withdrawal from drug: reversal of weight and hunger reduction during the double-blind placebo controlled withdrawal period.

Tertiary

To assess the effect of setmelanotide, over one year, on:

* Percent change in total body mass, non-bone lean mass, and bone density.

* Fasting lipid (cholesterol and triglyceride) panel.

* Pharmacokinetics of setmelanotide.

* C-reactive protein.

Dose response of setmelanotide through titration procedures.

* Changes in quality of life and health status.

Exploratory

To assess the effect of setmelanotide, over one year, on:

* Change in pubertal development for participants who have yet to reach Tanner Stage V.

* ABPM, skin pigmentation measured by spectrophotometer, energy expenditure, and 24-hour pharmacokinetic profile, only for patients participating in these sub-studies.

* Hormonal, neuroendocrine, metabolic and inflammatory analytes and biomarker assays.

* If identified, a pharmacokinetic/pharmacodynamics (PK/PD) response employing a suitable endocrine biomarker predictive of setmelanotide target engagement, agonism and efficacy through activation of the MC4R.

* If feasible, correlations of bi-allelic or loss-of-function LEPR genetic

mutations and LEPR deficiency due to diverse allelic variants with the

magnitude of setmelanotide efficacy endpoints.

Study description

Background summary

A genetic modification has been identified on the LEPR gene. These genes play a key role in the regulation of our body weight. Sometimes there is a genetic change (variation) in one of the genes responsible for the regulation of body weight. These genes are responsible for creating two messenger substances, (a-MSH or b-MSH), which are important for the feeling of being full (satiety) and the control of body weight. When there are variations in the LEPR genes, these genes do not function as they should and the messenger substances (MSH) are no longer produced. This can result in not feeling full and cause to eat too much and become overweight.
Rhythm Pharmaceuticals, Inc., the trial sponsor, developed the trial drug setmelanotide, a MSH messenger substance, which is hoped to replace the messenger substances that are missing in someone with a LEPR variation.
The drug is administered once a day by subcutaneous injection (under the skin). The daily injections can be performed at home. There will also be home health practitioners who are able to assist with the injections at home if required.
The drug has been tested in approximately 200 overweight and obese healthy patients (phase 1 and 2 clinical trials). This study is being done to check if the medicine works and is safe. If this is the case, then the medicine may be able to be approved for use in more patients.

Study objective

The main purpose of this trial is to find out if an investigational drug called setmelanotide (RM-493), which mimics MSH, can help control body weight. The efficacy of setmelanotide will be compared to the efficacy of a placebo during 4 to 8 weeks.

Study design

The drug is administered once a day by subcutaneous injection (under the skin). The daily injections can be performed at home. There will also be home health practitioners who are able to assist with the injections at home if

required.

Intervention

-patient questionnaires
-blood sampling for PK purpose
Sub-studies (if consented by patient):
24-hour pharmacokinetic study
Ambulatory blood pressure monitoring
Energy expenditure assessment
Quantitative skin colour measurement
Photographic skin assessment

Study burden and risks

Overall, setmelanotide has been generally well-tolerated in previous studies. Drug-Related Treatment Emergency AEs (for which the adverse event was assessed as possibly or probably related to study drug by the investigator) were reported. Because very few studies have been done using setmelanotide, there may be other unknown side effects. The PIs (or a covering clinician) will be available at all times to study participants in the event of a clinical emergency; both this availability and how to reach the investigators in an emergency will be clearly communicated orally and in writing to study participants. All study interventions will be provided free of cost. Please refer to the current Investigator*s Brochure for a comprehensive summary of the AEs reported to date.

Contacts

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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. Bi-allelic, homozygous or compound heterozygous (a;different gene mutation on each allele) genetic status for either the LEPR genes, with the ;loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.;2. Age 12 years and above.;3. If adult age *18 years, obesity with body mass index (BMI);* 30 kg/m2; if child or adolescent, obesity with weight > 97th percentile for age on growth chart assessment.;4. Study participant and/or parent or guardian can communicate well with the investigator, to understand and comply with the requirements of the study, and can understand and sign the written ;informed consent/assent, after being informed about the study.;5. Female participants of child-bearing potential must 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) or post- menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal lab range), ;or failure to have progressed to Tanner Stage V and/or 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 weight loss or weight stabilization. Patients may be reconsidered approximately 1 month ;after cessation of such intensive regimens.;2. 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 ;Rhythm prior to enrollment.;3. 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 study compliance.;4. A Patient Health Questionnaire-9 (PHQ-9) score of * 15.;5. 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.;6. Current, severe stable restrictive or obstructive lung disease due to extreme obesity, evidence of significant heart failure (NYHA Class 3 or greater), or oncologic disease, if these were severe enough to interfere with the study and/or would confound the results. Any such patients should be discussed with the sponsor prior to inclusion.;7. History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver tests [as indicated by abnormal liver function tests, alanine transaminase (ALT), ;aspartate transaminase (AST), alkaline phosphatase, or serum bilirubin (> 2.0 x upper limit of normal (ULN) for any of these tests)] for an etiology other than non-alcoholic 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 will be exclusionary, but the presence of NAFLD would not be exclusionary.;8. History or presence of impaired renal function as indicated by clinically significant abnormal creatinine, blood urea nitrogen (BUN), or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by the Cockcroft Gault equation < 30 mL/min.;9. History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism.;10. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, 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 study.;11. Volunteer is, in the opinion of the Study Investigator, not suitable to participate in the study.;12. Participation in any clinical study with an investigational drug/device within 3 months prior to the first day of dosing.;13. Significant hypersensitivity to study drug.;14. Inability to comply with QD injection regimen.;15. Patients who have been placed in an institution through and official or court order, as well as those who are dependent on the sponsor, Investigator, or study site.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2018
Enrollment:	3
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	06-09-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-12-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2020
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	EUCTR2017-002005-36-NL
CCMO	NL62288.078.17