A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial: Multiple Independent Sub-studies of Setmelanotide in Patients with POMC/PCSK1, LEPR, NCOA1 (SRC1) or SH2B1 Gene Variants in the Melanocortin-4 Receptor Pathway

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This study has been transitioned to CTIS with ID 2023-507634-24-00 check the CTIS register for the current data. To evaluate the efficacy of setmelanotide on changes in body weight.

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

Summary

ID

NL-OMON53452

Source
ToetsingOnline

Brief title
RM-493-035

Condition

- Metabolic and nutritional disorders congenital

Synonym
Gene defects, obesity

Research involving
Human

Sponsors and support

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

Intervention

Keyword: genetic defects, Obesity

Outcome measures

Primary outcome

To evaluate the efficacy of setmelanotide on changes in body weight.

Secondary outcome

• To evaluate the efficacy of setmelanotide based on the portion of patients

with a clinically meaningful decrease in body weight defined as >=5% decrease

from baseline

• To evaluate the efficacy of setmelanotide on changes in body weight in adult

patients with obesity

• To evaluate changes in hunger score in response to setmelanotide from

baseline to 52 weeks of treatment

• To evaluate the efficacy of setmelanotide on the portion of patients with at

least 10% decrease in body weight

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

This study has been transitioned to CTIS with ID 2023-507634-24-00 check the CTIS register for the current data.

To evaluate the efficacy of setmelanotide on changes in body weight.

Study design

This master protocol describes multiple, independent, randomized, double-blind, placebo-controlled, sub-studies of setmelanotide in patients with obesity with 6 specific gene defects in the melanocortin-4 receptor (MC4R) pathway:

• pro-opiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1) (Sub-study 035a)
• leptin receptor (LEPR) (Sub-study 035b)
• nuclear receptor coactivator-1 (NCOA1), also reffered to as steroid receptor coactivator-1 (SRC1) (Sub-study 035c)
• SRC homology 2 B adapter protein 1 (SH2B1) (Sub-study 035d)

These multiple sub-studies have a high degree of similarities. The objectives and endpoints are identical for all 5 sub-studies in patients with POMC and/or PCSK1 (Sub-study 035a), LEPR (Sub-study 035b), NCOA1 (SRC1) (Sub-study 035c) and SH2B1 (Sub-study 035d) gene variants in the MC4R pathway.

Intervention

Setmelanotide, 10 mg/mL in a sterile solution for injection.
Following randomization, patients will self-inject (or the caregiver will inject the patient) SC study drug daily for approximately 52 weeks.

Study burden and risks

The very common side effects that have been reported in >=10% of patients (10 or more out of 100 patients) who were taking setmelanotide include:

• Skin darkening or discoloration (generalized or local skin tanning or darkening of pre-existing moles or new benign moles)
• Nausea
• Vomiting
• Headache
• Injection site reactions such as pain, itching, redness, or skin hardening
• Increased intermittent/spontaneous penile erections (in male patients)

Blood tests, ECG, subcutaneous injection related risks, skin biopsy risks (only if requested by a dermatologist), discomfort and confrontation caused by certain questions in the questionnaires.

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)

Inclusion criteria

1. Patients must have a pre-identified:
• Heterozygous gene variant in the POMC gene or PCSK1 gene (Substudy035a),
• Heterozygous gene variant in the LEPR gene (Sub-study 035b),
• Homozygous, heterozygous, or compound heterozygous variant in the NCOA1 (SRC1) gene (Sub-study 035c),
• Homozygous, heterozygous, or compound heterozygous variant in the SH2B1 gene, or chromosomal 16p11.2 deletion encompassing the SH2B1 gene (Sub-study 035d),
For POMC, PCSK1, LEPR, NCOA1 (SRC1) and SH2B1 gene variants, to be considered for inclusion, the variant must either:
• Be categorized by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP)/International Organisation for Standardization (ISO) 15189 -certified laboratory using ACMG criteria as
a) pathogenic (P); or
b) likely pathogenic (LP); or

c) Variant of uncertain significance (VUS); or FOR POMC, PCSK1
d) and LEPR, in addition to P/LP, only the subcategory of VUS variants that are suspected to be pathogenic (VUS-SP) will be eligible for inclusion.
If a patient has 2 or more variants eligible for the trial, she/he will be assigned to a sub-study according to the following 2 rules:
1) To the highest ACMG pathogenicity category according to the following hierarchy: P > LP > VUS-SP > VUS (see Appendix 1 for further examples).
• For example, if a patient carries both a POMC pathogenic (P) variant and a LEPR VUS-SP variant, the patient will be assigned as a POMC Pathogenic (P) patient (Sub-study 035a).
2) If the 2 variants have the same ACMG classification, the patient will be assigned to the sub-study with lower overall frequency of gene variants according to the following hierarchy (least frequent to most frequent): LEPR > POMC/PCSK1 > NCOA1 (SRC1) > SH2B1 (see Appendix 2. for further examples).
For example:
• If a patient carries both a LEPR Pathogenic (P) variant and SH2B1 Pathogenic (P) variant, the patient will be assigned as a LEPR Pathogenic (P) patient (Sub-study 035b).
See Appendix 3 for genetic testing requirements to be enrolled in the trial.
2. Between 6 and 65 years of age at the time of provision of informed consent/assent.
3. Obesity, with reported onset in childhood, and BMI >=30 kg/m2 for patients >=18 years of age or BMI >=95th percentile for age and gender for patients 6 to 17 years of age, based on the United States (US) CDC criteria, at screening.
4. Patient and/or parent or guardian is able to communicate well with the Investigator, understand and comply with the requirements of the trial (including once daily [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 into the trial.
5. Patient and/or parent or guardian reports that the patient experienced childhood obesity, defined as the patient and/or parent or guardian reporting that the patient had obesity or was significantly overweight prior to the age of 6 years old.
Refer to the protocol for inclusion criteria 6, 7, and 8 due character limit.

Exclusion criteria

1. 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.
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. 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.
4. 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, or any suicidal behavior in the last month, or a Patient Health Questionnaire-9 (PHQ-9) score of >=15 during Screening.
5. 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.
6. HbA1c >10% at Screening.
7. 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.)
8. 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 to calculate eGFR (see Section 7.2.5).
9. History or close family history (parents or siblings) of melanoma, or patient history of oculocutaneous albinism.
10. Significant dermatologic findings relating to melanoma or premelanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. 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.
11. Patient is, in the opinion of the Investigator, not suitable to participate in the trial.
12. 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.
13. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
14. Hypersensitivity to the active substance or to any of the excipients of the investigational medicinal products (active and placebo).
15.Females who are, pregnant or breastfeeding, or planning or desiring to become pregnant during the duration of the trial.
16. Patients with the following gene variations: biallelic BBS (and/or clinical diagnosis of Bardet-Biedl syndrome [BBS]) or biallelic ALMS1, or any MC4R variants.
17. Legally protected persons per local regulations (e.g., those that fall under the L1121-6 article of the Public Health code in France) or other applicable local laws.

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:	Recruiting
Start date (anticipated):	08-12-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Setmelanotide
Generic name:	Setmelanotide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2023
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2024
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
EU-CTR	CTIS2023-507634-24-00
EudraCT	EUCTR2021-002873-24-NL
ClinicalTrials.gov	NCT05093634
CCMO	NL79961.078.22