A Phase 3, Randomized, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) with a Crossover to Open-Label Once Weekly Setmelanotide in Patients with Specific Gene Defects in the Melanocortin-4 Receptor Pathway Who Are Currently on a Stable Dose of the Once Daily Formulation

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Primary: To compare the pharmacokinetics (PK) of the once daily (QD) and once weekly (QW) formulations of setmelanotideSecondary Objectives:To assess the safety of the QW formulation of setmelanotide with up to 6 months (26 weeks) of drug...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON53772

Source
ToetsingOnline

Brief title
Setmelanotide - Daily vs weekly with crossover to open label

Condition

- Inborn errors of metabolism

Synonym
genetic mutation, Obesity

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Daily dosing, Genetic Obesity, Setmelanotide, Weekly dosing

Outcome measures

Primary outcome

Comparison of steady-state PK parameters (maximum plasma concentration [Cmax,], time to maximum plasma concentration [Tmax], trough plasma concentration [Ctrough], area under the plasma concentration-time curve over the dosing interval [AUC0-tau]) for QW compared with QD setmelanotide

Secondary outcome

Secondary endpoints :

Safety outcomes, including AEs/SAEs, ISRs and changes in laboratory parameters, vital signs, ECG recordings, and physical examination findings, etc.

Exploratory endpoints:

Proportion of patients who achieve the following change in body mass index (BMI) from baseline to Week 14 for QW vs QD setmelanotide groups:

1. > -2.5% and < 2.5% change

2. equal or more than 2.5% increase

3. equal or more than 2.5% decrease

Change and percent change in BMI from baseline to Week 14 for QW vs QD setmelanotide groups, and for up to 6 months (26 weeks) for all patients

Change and percent change in body weight in adult patients >18 years of age, and change in BMI Z-score and change in percentage of 95th percentile of age- and sex-predicted BMI for patients <18 years of age, from baseline to Week 14 for QW vs QD setmelanotide groups, and for up to 6 months (26 weeks) for all patients.

Change from baseline to Week 14 for in the QW vs QD setmelanotide groups, and for up to 6 months (26 weeks) for all patients in:

- waist circumference,
- lipid levels, and
- HbA1c

Change in average daily most/worst hunger and global hunger scores from baseline to Week 14 for QW vs QD groups and for up to 6 months (26 weeks) for all patients.

Change in total score from baseline to Week 14 in Symptoms of Hyperphagia (patient/caregiver versions) for QW vs QD groups and for up to 6 months (26

weeks) for all patients.

Study description

Background summary

In a subset of individuals with obesity, rare genetic variants may result in severe obesity. The identification of key genetic determinants of the neuronal pathways and signaling molecules (e.g., leptin) regulating appetite and body weight has led to the discovery of multiple rare genetic disorders of obesity (RGDO). A key neuronal pathway, the central melanocortin and melanocortin-4 receptor (MC4R) pathway, plays an important role in appetite, hunger, and energy utilization. In humans and animal models, genetic defects in the MC4R pathway, such as POMC deficiency, result in severe forms of early-onset obesity and hyperphagia. Patients with rare genetic variants in leptin receptor (LEPR) and patients with Bardet-Biedl syndrome (BBS, a rare pleiotropic autosomal recessive disorder caused by mutations in as many as 24 different genes) also present with unremitting hunger and severe obesity caused in part by a lack of activation of the MC4R pathway. As a result of hyperphagia, individuals with RGDO have increased calorie intake leading to early-onset, severe obesity, and obesity-related comorbidities such as type 2 diabetes. The Sponsor is developing setmelanotide (also known as RM-493), an MC4R agonist, as a treatment for patients with RGDO. Setmelanotide bypasses upstream signaling defects to directly activate MC4R. The purpose of this study is to compare the QW and QD formulations of setmelanotide in patients with biallelic PPL (POMC [pro-opiomelanocortin], PCSK1 [proprotein convertase subtilisin/kexin Type 1], LEPR [leptin receptor]), heterozygous PPL, and patients with BBS. QW dosing is expected to provide a more convenient dosing regimen for these patients and would be more suitable for younger patients than QD dosing. In addition, QW dosing would be expected to improve compliance, especially given the long-term requirement for continued dose administration in order to achieve sustained benefits.

Study objective

Primary:
To compare the pharmacokinetics (PK) of the once daily (QD) and once weekly (QW) formulations of setmelanotide

Secondary Objectives:
To assess the safety of the QW formulation of setmelanotide with up to 6 months (26 weeks) of drug administration

Study design

This study is designed to compare the safety, pharmacokinetics (PK), and efficacy of the QW and QD formulations of setmelanotide, as well as to evaluate the safety and efficacy of up to 6 months of QW setmelanotide administration in patients with BBS, biallelic PPL, or heterozygous PPL. Eligible patients are those who are currently taking QD setmelanotide in Study RM-493-022, referred to as the long-term extension (LTE) study, for at least 6 months with acceptable safety and tolerability, and who wish to continue with setmelanotide treatment, and who otherwise meet all inclusion and exclusion criteria.
Approximately 30 patients will be targeted in 3 age groups as follows: approximately 20 patients >=18 years old; approximately 6 patients >=12 to <18 years old; and approximately 4 patients >=6 to <12 years old at the time of study entry.
The study consists of a Screening Period for transition from the LTE study, a Run-in Period of up to 1 week of continuation on the patient*s current dose level of QD setmelanotide (2, 2.5, or 3 mg), a 13-week double-blind phase in which the patients will be randomized to either QD or QW setmelanotide, a 13-week non-randomized open-label phase where all patients will receive open-label QW setmelanotide, and a 3-week follow-up period in which all patients will return to their run-in dose level of QD setmelanotide to prepare for re-enrollment into Study RM-493-022 or to resume the QD formulation in some other way.
The safety and tolerability of setmelanotide will be assessed by the frequency and severity of AEs/serious adverse events (SAEs) and ISRs, as well as changes in physical examinations (to include comprehensive skin examinations), electrocardiograms (ECGs), vital signs (including resting blood pressure [BP] and heart rate [HR]), routine laboratory evaluations, development of anti-drug antibodies (ADA), and the Columbia-Suicide Severity Rating Scale (C-SSRS).
Efficacy assessments include: body weight, Hunger Questions, Symptoms of Hyperphagia Questions, laboratory evaluations of lipids, glucose, and glycosylated hemoglobin (HbA1c), and waist circumference.

Intervention

Daily and/or weekly subcutaneous administration of setmelanotide from 2, 2,5 or 3 mg (QD) and 20, 25 or 30 mg (QW)
Venipunctures for blood determinations
Skin examination for suspicious lesions at screening, week 27 and week 30
Full physical examination at screening and End of Trial (EoT, week 30), a brief physical examination at the other visits.
An echocardiogram (heart film) at visit 1, visit 3, visit 11, visit 16, visit 20 and visit 21.
Parents are asked to complete daily hunger and hyperphagy questions in an electronic diary
Parents are asked to complete questionnaires on hunger and suicidal ideation.
Questionnaires on suicidal ideation at Visit 1, 2, 3, 7, 11, 16, 18, 19, 20 and 21.

Study burden and risks

In patients with RGDO, setmelanotide has been associated with clinically meaningful reductions in weight and improvement in hunger. In particular, in patients with POMC or LEPR deficiency obesity, who are characterized by early-onset obesity, severe hunger and progressive weight gain, setmelanotide has demonstrated clinically meaningful and statistically significant weight loss, setmelanotide has demonstrated clinically meaningful and statistically significant decreases in hunger. Both the decreased hunger and the weight loss continued over 52 weeks of treatment and are maintained with continued setmelanotide treatment. Furthermore, following the significant weight loss with setmelanotide treatment, there were improvements in lipids and other parameters, as well as body composition with decreased fat mass and decreased waist circumference. These weight loss changes were accompanied by improvements in quality of life.
Setmelanotide is well tolerated. Side effects of setmelanotide are predictable, well understood, and do not present significant safety concerns. Collectively, safety data obtained to date show that adverse events (AEs) commonly associated with setmelanotide include injection site reactions (ISRs) and skin hyperpigmentation. Less commonly, nausea and vomiting were reported and rarely, sexual AEs have been observed. Potential mechanistic-based events such as hypertension have been assessed throughout the setmelanotide clinical development program and have not been observed. Events associated with severe obesity such as depression and suicidal ideation occurred infrequently and were assessed as not related to setmelanotide.
Specifically, regarding children less than 12 years old, the AEs reported in this population were consistent with those reported in other studies of setmelanotide. Adverse events reported as related to setmelanotide treatment were consistent with the known safety profile. No evidence for concern regarding bone development has been observed. Three of the 4 patients showed progression into puberty.
Daily injection of setmelanotide is technically challenging for pediatric patients and patients with poor coordination/vision or other physical challenges, thus, the Sponsor is developing the weekly formulation to improve compliance and to address user limitations, with the assumption that safety and efficacy between the two formulations will be comparable.
In summary, setmelanotide has a positive benefit-risk profile in patients with genetic defects upstream of the MC4R and the QW formulation may have the added advantage of a more convenient dosing regimen.
More detailed information about the known and expected benefits and risks and reasonably expected AEs of setmelanotide may be found in the Investigator*s Brochure.

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.

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. All patients must have met the criteria for diagnosis of a gene defect in the MC4R pathway (BBS, biallelic PPL, heterozygous PPL), for which they are being treated with QD setmelanotide.
2. Patients must be >=6 years old at screening.
3. Patients must have been taking the setmelanotide QD formulation for at least 6 months in the LTE trial with acceptable safety and tolerability, and the dose

level must have been stable at 2, 2.5 or 3 mg of setmelanotide for at least the last 3 months prior to starting the Run-in Period.
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 and is able to understand and sign the written informed consent/assent.
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 8.8.7:
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (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 (FSH) level in the post-menopausal lab range) do not require contraception during the trial.
Younger female patients who have not achieved sexual maturity at study 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 of contraception if they become sexually active during the trial or within 90 days following their participation in the study.
Male patients must also not donate sperm during and for 90 days following their participation in the trial.

Exclusion criteria

1. HbA1C >9.0% at screening.
2. Has taken a medication that is approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) within 3 months prior to starting the Run-in Period. Glucagon-like peptide-1 (GLP) -1) receptor agonists being prescribed for the treatment of obesity are not allowed.

3. History of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests for an etiology other than nonalcoholic fatty liver disease (NAFLD). Thus, any underlying etiology besides NAFLD, including diagnosed nonalcoholic steatohepatitis (NASH), other causes of hepatitis, or history of hepatic cirrhosis is exclusionary, but the presence of NAFLD is not exclusionary.
4. Moderate to severe renal dysfunction as defined by a glomerular filtration rate <30 mL/min. (based upon the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation 2021 from the National Kidney Foundation). In patients <18 years of age the Bedside Schwartz Equation should be used to calculate estimated glomerular filtration rate (eGFR).
5. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by the Investigator during screening. Any concerning lesions identified during the Screening Period will be biopsied and results must be known to be benign prior to enrollment. If the pretreatment biopsy results are of concern, the patient should be excluded from the trial.
6. Diagnosis of schizophrenia, bipolar disorder, personality disorder, or other psychiatric disorders that the Investigator believes will interfere significantly with trial compliance. Neurocognitive disorders affecting ability to consent will not be disqualifying as long as an appropriate guardian able to give consent has been appointed.
7. Clinically significant depression or suicidality as defined by: any suicidal ideation of type 4 or 5 on the C SSRS, any lifetime history of a suicide attempt, or any suicidal behavior in the last month or a Patient Health Questionnaire-9 (PHQ-9) score of >=15 during Screening in patients with no significant neurocognitive deficits.
8. Patient is not suitable, in the opinion of the Investigator, to participate in the trial.
9. Hypersensitivity to the active substance or to any of the excipients of the investigational products (active or placebo).
10. Inability to comply with the QW and QD injection regimens.
11. Participation in any clinical trial with an investigational drug/device within 3 months prior to the first day of dosing, with the exception of a setmelanotide clinical trial.
12. 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.
13. The patient or a relative of the patient is the investigator or a sub investigator, research assistant, pharmacist, trial coordinator, or other staff directly involved with the conduct of the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-01-2023
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Setmelanotide (RM-493) QD
Generic name:	Setmelanotide (RM-493) QD
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Setmelanotide (RM-493) QW
Generic name:	Setmelanotide (RM-493) QW
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-03-2022
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2023
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	EUCTR2021-004597-65-NL
ClinicalTrials.gov	NCT05194124
CCMO	NL80213.078.22