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HEALTH TECHNOLOGY BRIEFING
MAY 2019

Setmelanotide for rare genetic obesity due to leptin receptor deficiency

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Developer/Company	Rhythm Pharmaceuticals Inc	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Setmelanotide is in clinical development for the treatment of rare genetic obesity due to leptin receptor deficiency. The leptin receptor is found on the surface of cells in many organs and tissues of the body, including a part of the brain called the hypothalamus, which controls hunger and thirst. The leptin receptor is involved in the control of body weight by increasing energy expenditure and reducing appetite. Individuals with leptin receptor deficiency experience excessive hunger and weight gain.

Setmelanotide is given as a sub-cutaneous (under the skin) injection. It is believed to restore lost activity of the leptin receptor, re-establishing weight and appetite control in patients. If licensed, setmelanotide will offer a treatment option for patients with obesity due to leptin receptor deficiency who currently have few effective therapies available.

PROPOSED INDICATION

Rare genetic obesity due to leptin receptor (LEPR) deficiency[1,a]

TECHNOLOGY

DESCRIPTION

Setmelanotide (RM-493) is a first-in-class melanocortin-4 receptor (MC4R) agonist which is in development for the treatment of rare genetic disorders of obesity.[2] The MC4R pathway plays a critical role in controlling food intake and energy expenditure. Variants in genes within the MC4R pathway, including the leptin and the leptin receptor (LEPR) genes, are associated with unrelenting hunger, known as hyperphagia, and severe, early-onset obesity. Leptin is a hormone released from white adipose tissue, which regulates appetite and energy expenditure in part through engagement of its cognate receptor, LEPR, expressed on arcuate nucleus proopiomelanocortin (POMC) neurons.[3] Setmelanotide is believed to restore lost activity in the MC4 pathway, re-establishing weight and appetite control in patients with these rare genetic disorders.[4]

Setmelanotide is in development for the treatment of rare genetic obesity caused by leptin receptor deficiency and is currently in phase III in clinical trials (NCT03287960 and NCT03651765). In these ongoing trials, setmelanotide solution for infusion 10mg/ml is administered via subcutaneous injection, once daily for eight weeks.[1,5-7]

INNOVATION AND/OR ADVANTAGES

Until recently, therapeutics for modulation of the MC4R pathway only included leptin administration for leptin-deficient patients. Efforts to treat rare genetic obesity with first-generation MC4R agonists revealed limited efficacy and were accompanied by adverse side effects, including increased blood pressure and heart rate. Setmelanotide, a second-generation MC4R agonist, has shown to reduce hyperphagia and body weight without occurrence of severe side effects. Furthermore, compared to formerly developed and tested MC4R agonists, setmelanotide has the unique capability of activating nuclear factor of activated T cell (NFAT) signalling and restoring function of this signalling pathway for selected MC4R variants.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Setmelanotide does not currently have Marketing Authorisation in the EU/UK for any indication.

- Setmelanotide has been granted orphan drug designation in the EU in November 2018 for the treatment of leptin receptor deficiency.[9]

- Setmelanotide has been granted PRIority MEdicines (PRIME) Designation in July 2018 for the treatment of obesity associated with pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity by the European Medicines Agency (EMA).[10,11]

Setmelanotide is in phase III clinical development for:

- Patients with rare genetic disorders of obesity (including POMC deficiency, LEPR deficiency, Bardet-Biedl syndrome and Alström syndrome)[12]
- Bardet-Biedl Syndrome and Alström Syndrome patients with moderate to severe obesity[13]

[a] Information provided by Rhythm Pharmaceuticals Inc

- Early-onset POMC deficiency obesity[14]

PATIENT GROUP

DISEASE BACKGROUND

Leptin receptor (LEPR) deficiency is caused by mutations in the LEPR gene. This gene provides instructions for making a protein called the LEPR, which is involved in the regulation of body weight. The LEPR protein is found on the surface of cells in many organs and tissues of the body including a part of the brain called the hypothalamus. The hypothalamus controls hunger and thirst as well as other functions such as sleep, moods, and body temperature. It also regulates the release of many hormones that have functions throughout the body.[15,16]

The LEPR is turned on (activated) by a hormone called leptin that attaches (binds) to the receptor. Normally, the body's fat cells release leptin in proportion to their size. As fat cells become larger, they produce more leptin. This rise in leptin indicates that fat stores are increasing. In the hypothalamus, the binding of leptin to its receptor triggers a series of chemical signals that affect hunger and help produce a feeling of fullness.[15,16]

LEPR gene mutations cause LEPR deficiency prevent the receptor from responding to leptin, leading to the excessive hunger and weight gain associated with this disorder.[15,16]

LEPR deficiency is an inherited disease that causes severe obesity beginning in the first few months of life. Affected individuals are of normal weight at birth. The extreme hunger leads to chronic excessive eating (hyperphagia) and obesity. Affected individuals develop abnormal eating behaviours such as fighting with other children over food, hoarding food, and eating in secret.[15,16]

LEPR deficiency is a long-term debilitating and life-threatening disease because it leads to severe obesity and related complications.[17]Rare genetic obesity is often comorbid with conditions such as osteoarthritis and lower back pain, illnesses that can result in functional locomotor limitations. The presence of pain can affect the global sense of well-being, quality of life and overall functional capacity, leading to decreased physical activity. As a consequence, a vicious cycle emerges where the presence of factors such as pain and immobility issues limit a person's ability to engage in activities that are important for personal satisfaction.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Single gene mutations leading to severe obesity have so far been identified in 3-5% of cases in European populations.[19] In November 2018, leptin receptor deficiency affected approximately 0.1 in 10,000 people in the European Union, which was equivalent to a total of around 5,000 people.[17] There are seven known patients in England with congenital leptin deficiency.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Children with untreated congenital leptin deficiency are likely to present to local paediatric or obesity services, because of the behavioural disturbance associated with uncontrolled appetite or because of severe obesity. The proposed pathway is from local paediatric or obesity services to an expert centre with experience in the diagnosis and treatment of genetic disorders of obesity.

Adult patients will present to local obesity services (most will be patients with untreated disease moving to England from other countries). Such patients will be referred from local obesity services to an expert centre with experience in the diagnosis and treatment of genetic disorders of obesity.[20]

CURRENT TREATMENT OPTIONS

In 2018, NHS England published guidelines to commission metreleptin treatment for patients with congenital leptin deficiency. Metreleptin is an artificial form of leptin. It replaces the hormone which is missing.[20]

PLACE OF TECHNOLOGY

If licensed, setmelanotide will offer an additional treatment option for patients with rare genetic obesity due to leptin receptor deficiency who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03287960, EudraCT- 2017-002005-36, **RM-493-015; aged ≥12 years; setmelanotide vs placebo; phase III**	NCT03651765, EUdraCT-2017-005006-35, **RM-493-022; setmelanotide; phase III extension**
Sponsor	Rhythm Pharmaceuticals, Inc.	Rhythm Pharmaceuticals, Inc.
Status	Ongoing	Ongoing
Source of Information	Trial registry[1,6]	Trial registry[5,7]
Location	Four EU countries (incl UK) and the USA	Germany, United States
Design	Open-label with an 8 week double-blind placebo-controlled withdrawal period	Open-label, single group assignment
Participants	n=10 (estimated); aged ≥12 years; bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for the LEPR gene, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype	n=100 (estimated); aged ≥6 years; Completed participation (all critical study evaluations) on active drug in a previous setmelanotide study for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway
Schedule	Assigned to subcutaneous injection of setmelanotide (10 mg/ml) once daily or placebo subcutaneous injection once daily. During the double blind placebo withdrawal period, patients will receive setmelanotide or placebo at variable times over an 8 week period.	Assigned to subcutaneous injection of setmelanotide (10 mg/ml) once daily
Follow-up	Follow-up 8 weeks and 1 year	Follow-up 2 years
Primary Outcomes	Weight loss [Time Frame: 1 year]	Safety and tolerability of setmelanotide [Time Frame: 2 years]
Secondary Outcomes	**Time frame 8 weeks:**	**Time Frame: 2 years:** - Weight loss

	- Reversal of weight during the double-blind placebo controlled withdrawal phase - Assessment of weight regain during the double-blind withdrawal phase **<u>Time frame 1 year:</u>** - Incidence of Treatment-Emergent Adverse Events - Body Fat Mass - Hunger - Assessment of fasting glucose, glycated hemoglobin (HbA1c) and oral glucose tolerance test (OGTT) - Waist circumference - Assessment of waist circumference	- Hunger - Body fat mass - Waist circumference - Percent change in total body mass, non-bone lean mass, and bone density - Lipid Labs - Assessment of Quality of Life - Assessment of Health Status - Biomarker Assays
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Primary completion date reported as December 2019	Primary completion date reported as March 2023

ESTIMATED COST

The cost of setmelanotide is not yet known

RELEVANT GUIDANCE

NICE GUIDANCE

NICE clinical guideline. Obesity: identification, assessment and management (CG189). November 2014.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

NHS England. Clinical Commissioning Policy: Metreleptin for congenital leptin deficiency (all ages). 170095P. December 2018.

OTHER GUIDANCE

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. 2015.[21]

ADDITIONAL INFORMATION

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