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Setmelanotide for pro-opiomelanocortin deficiency obesity

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LAY SUMMARY

Body fat and food intake are regulated by signals from the brain to the gut. One of the important hormones that is responsible for this is pro-opiomelanocortin (POMC). In a very small group of people there is a lack of this hormone (due to a genetic mutation), referred to as POMC deficiency. This causes severe overeating which leads to obesity and high blood sugar in children. Very few adults have been observed with this condition, which may be due to high death rates in adolescence. Pale skin that does not tan and red hair are common signs of POMC deficiency obesity.

Currently there are no licensed treatment options for POMC deficiency obesity, however weight loss medicines orlistat and methylcellulose are the only treatment options offered. Setmelanotide is being developed to treat pro-opiomelanocortin (POMC) deficiency obesity. If marketed setmelanotide could be the first effective treatment option aimed specifically at this patient group as it replaces one of the key hormones that is lacking in POMC deficiency patients (melanocyte-stimulating hormone). It has been shown to reduce hunger and has resulted in substantial weight loss in previous patients.

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TARGET GROUP

Pro-opiomelanocortin (POMC) deficiency obesity

TECHNOLOGY

DESCRIPTION

Setmelanotide (RM-493) is a first-in-class peptide that acts by targeting the melanocortin 4 receptor (MC4R) which is encoded by the MC4R gene. MC4R encodes the MC4 protein, a G-protein coupled receptor that binds to α-melanocyte stimulating hormone (α-MSH) which acts by activating the MC4R, resulting in a decrease in food intake.[1] The MC4 pathway is a key pathway in humans that regulates energy expenditure, homeostasis, and appetite, therefore activation of the MC4R can potentially alleviate some of the health risks associated with obesity.[2]

Setmelanotide is under development for the treatment of POMC deficiency obesity and is currently in phase II/III clinical trials. It is administered via subcutaneous injection, once daily for one year.[3]

Setmelanotide is also currently in a phase II/III clinical trial for rare genetic obesity conditions: LepR deficiency obesity, Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome and POMC heterozygous deficiency obesity.[4]

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

INNOVATION and/or ADVANTAGES

As patients with POMC deficiency obesity have stunted levels of melanocyte-stimulating hormone,[5] setmelanotide acts to replace this deficient hormone.[6] Additionally results from a phase II clinical trial where severely obese patients with POMC deficiency were given setmelanotide over the course of 12 weeks and 42 weeks, respectively, indicate significant reductions in hunger and substantial weight loss.[5] As there are currently no viable treatment options for this patient group, setmelanotide could prove to be an effective and novel treatment method.[6]

DEVELOPER

Rhythm Pharmaceuticals Inc.

AVAILABILITY, LAUNCH or MARKETING

Setmelanotide was designated Orphan Drug Status in the EU in 2016 for pro-opiomelanocortin deficiency.[6]

Setmelantoide was designated Fast Track Status and Orphan Drug Status by the FDA, in 2016 for pro-opiomelanocortin deficiency obesity.[7]

The company's current licensing plans were unavailable.

PATIENT GROUP

BACKGROUND

Body adiposity, energy intake and energy expenditure are regulated homeostatically by neural and hormonal signals between the brain and the gut.[8] One of the hormones considered crucial in the regulation of energy expenditure and satiety is POMC, which if deficient in humans, leads to severe obesity (referred to as POMC deficiency obesity).[5] POMC deficiency is inherited in an autosomal recessive manner and begins in early infancy, characterised by constant hunger, excessive eating and weight gain.[6,9] Whilst a normal weight at birth is usually achieved, by 1 year old, severe obesity occurs at this age.[9]

Complete POMC deficiency is caused by homozygous or compound heterozygous loss-of-function mutations in the POMC gene. POMC is regulated by leptin and is cleaved by prohormone convertases to produce the melanocortin receptor ligands; adrenocorticotrophin (ACTH), α-MSH and β-melanocyte-stimulating hormone (β-MSH).[7] As a result of POMC deficiency, there is a shortage of the peptides made from POMC, including ACTH, α-MSH, and β-MSH. Without ACTH, there is a reduction in cortisol production, leading to adrenal insufficiency.[9] Additionally hypocortisolism is associated with hypoglycaemia, hyperbilirubinemia and cholestasis, in neonatals.[5] Decreased α-MSH in the skin reduces pigment production, resulting in the red hair and Fitzpatrick type 1 skin often seen in people with POMC deficiency. Furthermore, a reduction of α-MSH and β-MSH in the brain dysregulates the body's energy balance, leading to hyperphagia and severe obesity.[9] Additionally, POMC deficiency patients with PCSK1 mutations may exhibit a history of malabsorption in infancy or a history of diarrhoea.[10]

It remains unclear as to whether patients with POMC deficiency have increased risks of weight-related cardiovascular disease, type 2 diabetes, and other obesity-related conditions. Although, the absence of older adult patients with POMC deficiency may elucidate a high mortality in earlier adulthood.[5]

CLINICAL NEED and BURDEN OF DISEASE

POMC deficiency is an extremely rare disease although its prevalence is believed to be underestimated.[11] Fewer than 50 affected cases have been reported globally,[11] whilst estimates suggest that <1 /1,000, 000 people are affected by the condition.[7] In the European Union, POMC deficiency is estimated to impact less than 0.1 in 10,000 people.[6]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance available

NHS ENGLAND and POLICY GUIDANCE

No guidance available

OTHER GUIDANCE

Challis, B. and Millington, G. Gene Reviews - Proopiomelanocortin Deficiency. Available from: https://www.ncbi.nlm.nih.gov/books/NBK174451/ [Accessed 30 August 2017]

CURRENT TREATMENT OPTIONS

There are no targeted treatments for POMC deficiency, but patients are currently treated with the weight loss medicines orlistat and methylcellulose.[6]

The symptoms related to the lack of ACTH can be fully reversed with hydrocortisone. However, the early-onset obesity and hyperphagia can only be treated symptomatically, with very limited success.[12]

EFFICACY and SAFETY

Trial	NCT02896192; setmelanotide vs placebo; phase II/III
Sponsor	Rhythm Pharmaceuticals Inc.
Status	Ongoing
Source of Information	Trial registry[3]
Location	Three EU countries incl UK
Design	Interventional/non-randomised/open-label study
Participants	n=25 (planned); aged ≥ 12 years old; bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for either the POMC or PCSK1 genes, with the loss-of-function (LOF) variant for each allele conferring a severe obesity phenotype.
Schedule	Subjects are assigned to one of two arms. Subjects receive either a setmelanotide subcutaneous injection once daily for one year or subjects receive placebo subcutaneous injection once daily. During the double blind placebo withdrawal period subjects receive placebo at variable times over an 8 week period in order for subjects to serve as their own control.
Follow-up	Not reported
Primary Outcomes	Measurement of the effect of setmelanotide on weight loss [time frame: 1 year]
Secondary Outcomes	Assessment of adverse events related to treatment [time frame: 1 year] Assessment of body composition as measured by bioelectrical impedance (BIA) or dual-energy x-ray absorptiometry (DXA) [time frame: 1 year] Assessment of hunger using a hunger questionnaire [time frame: 1 year] Assessment of fasting glucose, glycated haemoglobin (HbA1c), and oral glucose tolerance test (OGTT) [time frame: 1 year] Assessment of waist circumference [time frame: 1 year] Assessment of weight regain during the withdrawal phase [time frame: 8 weeks] Non-bone lean mass
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as October 2018.

ESTIMATED COST and IMPACT

COST

The cost of setmelanotide is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers, improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment)*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Information received from Rhythm Pharmaceuticals

Rhythm Pharmaceuticals Inc did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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