NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Setmelanotide for treating obesity caused by rare genetic disorders in children aged 2 to 6 years

Company/Developer	Rhythm Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33635	NICE ID: 11827	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Setmelanotide is in clinical development for the treatment of children aged 2 to <6 years with obesity caused by rare genetic disorders. These include proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS), all of which are characterised by early-onset hyperphagia and resulting obesity. Obesity is defined as abnormal or excessive fat build up that may cause poor health. Childhood obesity has many influencing factors, but essentially is caused by taking in more energy than is used over time. Behavioural, environmental, and genetic risk factors can be responsible for causing obesity. Currently there are no licensed pharmacological interventions for children aged 2 to 6 years with obesity in the UK.

Setmelanotide is a selective melanocortin-4 receptor (MC4R) agonist. MC4Rs in the brain are involved in regulation of hunger, satiety, and energy expenditure. Setmelanotide is believed to re-establish MC4R pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure. It would be administered as an injection under the skin. If setmelanotide is licensed, it could offer a treatment option for children with obesity caused by a rare genetic condition.

Proposed Indication

Treatment of children aged 2 to <6 years with obesity caused by a rare genetic disorder including: proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS).[1]

Technology

Description

Setmelanotide (Imcivree) is a selective melanocortin-4 receptor (MC4R) agonist. MC4Rs in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4R, setmelanotide is believed to re-establish MC4R pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.[2]

Setmelanotide is in clinical development for the treatment of paediatric obesity caused by rare genetic disorders. In the phase III trial (NCT04966741), setmelanotide is administered as a subcutaneous (SC) injection at a starting dose of 0.5 mg per day. Dose can be increased by 0.5mg increments, every 2 weeks, until reaching the target maximum dose (not to exceed 2mg daily).[1]

Key Innovation

Current management for general obesity (best supportive care) focuses on dietary restrictions and lifestyle changes, including exercise.[3] 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.[4] In previous phase III trials, setmelanotide led to improved quality of life (QOL) in patients as early as week 5, with some patients no longer experiencing impaired QOL at week 52.[5]

If approved, setmelanotide will provide a novel treatment option for very young children from age 2 to <6 years, allowing patients with impaired MC4R pathway to be treated earlier in life.

Regulatory & Development Status

Setmelanotide is currently licensed in the UK for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above.[2]

Setmelanotide is currently in phase II and III clinical trials for the treatment of obesity also caused by Smith-Magenis Syndrome, ML4R deficiency and defects in leptin-melanocortin pathway.[6]

Setmelanotide has the following regulatory designations/awards:

- An Orphan Drug in the EU in August 2019 for the treatment of BBS.[7]
- An Orphan Drug in the EU in November 2018 for the treatment of LEPR deficiency.[8]
- An Orphan Drug in the EU in July 2016 for the treatment of POMC deficiency.[9]
- A PRIME status for treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R pathway in June 2018.[10]

Patient Group

Disease Area and Clinical Need

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.[11] A BMI ≥95th percentile (or ≥ to 30 kg/m^2, whichever is lower) is defined as obesity.[12] POMC and LEPR deficiencies are rare genetic disorders of obesity that severely affect the QOL of people with them, and their families and caregivers. They cause early onset, severe obesity and hyperphagia (characterised by a feeling similar to starvation) and are linked with many chronic conditions. They are also likely to shorten life expectancy.[3] A rare mutation in the *PCSK1* gene leads to a proconvertase 1 deficiency, which is an enzyme involved in the maturation of insulin, and this can cause obesity. BBS is a highly heterogeneous disease. It is characterised by severe early-onset obesity, amongst other conditions.[13] Like adult obesity, childhood obesity has many influencing factors, but essentially is caused by taking in more energy than is expended over a period of time.[14] Behavioural and environmental factors are often primarily responsible, although genes can play an important role in regulation of body weight. Other risk factors include a diet containing high levels of fat or sugar, lack of exercise, psychological issues, socioeconomic factors, and certain medications. Childhood obesity often causes complications in a child's physical, social and emotional well-being.[15]

39 million children under the age of 5 were overweight or obese in 2020, worldwide.[11] In England, 14.4% of reception age children (age 4-5) are obese, with a further 13.3% overweight (2020/21). Children living in deprived areas are substantially more likely to be obese.[16] Today, more than 1 in 3 children in the UK suffer with overweight or obesity. Research suggests that, if untreated, 85% of these children will continue to suffer with obesity into adulthood. In the UK, 19% of children (2.5 million) are obese.[14] In England (2021-22), there were 8,976 finished consultant episodes (FCEs) and 7,876 admissions for a primary diagnosis of Obesity (ICD-10 code E66), which resulted in 1,770 day cases and 18,589 FCE bed days for all ages. There were 34 patients aged 1-4 years, and 132 patients aged 5-9 years with a primary diagnosis of obesity.[17]

Recommended Treatment Options

NICE currently recommend lifestyle interventions, behavioural interventions, physical activity and dietary approaches first to treat childhood general obesity.[18]

Drug treatment is not generally recommended for children younger than 12 years. In children younger than 12 years, NICE recommends that drug treatment may be used only in exceptional circumstances, if severe comorbidities are present. Prescribing should be started and monitored only in specialist paediatric settings.[18]

Clinical Trial Information

Trial	NCT04966741; EudraCT- 2021-004167-27; A Phase 3 Multi-Center, One-Year, Open-Label Study of Setmelanotide in Pediatric Patients Aged 2 to <6 Years of Age With Rare Genetic Causes of Obesity **Phase III –** Active, not recruiting **Location(s) –** Spain, UK, US, and Australia **Primary completion date –** September 2023
Trial Design	Single group assignment, open label

Population	N = 12 (actual); obesity due to POMC, PCSK1, or LEPR deficiency, or BBS; 2 years to 5 years; BMI ≥97th percentile
Intervention(s)	Setmelanotide SC injection
Comparator(s)	No comparator
Outcome(s)	**Primary outcomes:** • Proportion of patients demonstrating >0.2 decrease from baseline in body weight [Time Frame: 1 year] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The list price of setmelanotide is £2,376.00 per 10 mg per ml vial for injection (excluding VAT; company's evidence submission).[19]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Obesity: identification, assessment and management (CG189). September 2022.
- NICE clinical guideline. Obesity prevention (CG43). March 2015.
- NICE guideline. Preventing excess weight gain (NG7). March 2015.
- NICE quality standard. Obesity: clinical assessment and management (QS127). August 2016.
- NICE quality standard. Obesity in children and young people: prevention and lifestyle weight management programmes (QS94). July 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Obesity surgery for children with severe complex obesity. 16053/P. April 2017.
- NHS England. 2013/14 NHS Standard Contract for Bardet-Biedl Syndrome Service (All Ages). A17/S(HSS)f.
- NHS England. 2013/14 NHS Standard Contract for Severe and Complex Obesity (All Ages). A05/S/a.

Other Guidance

- American Psychological Association. Clinical Practice Guideline for Multicomponent Behavioural Treatment of Obesity and Overweight in Children and Adolescents. 2018.[20]
- Endocrine Society. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. March 2017.[21]
- The Danish Paediatric Society. Danish clinical guidelines for examination and treatment of overweight and obese children and adolescents in a pediatric setting. 2015.[22]
- National Health & Medical Research Council (NHMRC). Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. 2013.[23]

- Scottish Intercollegiate Guidelines Network (SIGN). Management of Obesity - A national clinical guideline. February 2010.[24]

Additional Information

Rhythm Pharmaceuticals 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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