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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2021

Setmelanotide for obesity in Bardet-Biedl syndrome and Alström syndrome

NIHRIO ID	26901	**NICE ID**	10315
Developer/Company	Rhythm Pharmaceuticals	**UKPS ID**	Not Applicable

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Setmelanotide is in clinical development as a first-line treatment for patients with Bardet-Biedl Syndrome (BBS) and Alström Syndrome (AS) who develop an increased appetite (hyperphagia) and are obese. BBS and AS are genetic conditions that impact multiple body systems. Both syndromes are caused by genetic mutations that are usually inherited from their parents. Obesity is a key symptom of both syndromes. The current treatment option is limited to only managing symptoms; no pharmacological options are currently available.

Setmelanotide is a protein that binds to a specific receptor to activate areas in the brain that control appetite. This reduces hunger sensations and therefore obesity. This is important in BBS and AS as obesity and hyperphagia are symptoms in both syndromes and these conditions can have damaging effects on the health of patients. If licensed, setmelanotide, given as an injection under the skin, will offer a first pharmacological treatment for BBS and AS.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Patients aged 6 years and older with hyperphagia and moderate to severe obesity in Bardet-Beidl syndrome (BBS) or Alström syndrome (AS).[1]

TECHNOLOGY

DESCRIPTION

Setmelanotide (RM-493, BIM-22493) is a synthetic cyclic peptide that preferentially binds to human melocortin-4 receptor (MC4R) with high affinity and activates MC4R at nanomolar concentrations.[2] It acts as a substitute for melanocyte stimulating hormone for MC4R-expressing neurons.[3,4] It is designed to restore impaired MC4R pathway function caused by genetic variants that occur upstream of the MC4R. It has the potential to affect weight loss by activating hypothalamic centres in the brain that control appetite which subsequently leads to reduced hunger.[2]

In the phase III clinical trial (NCT03746522), setmelanotide 3mg was given daily via subcutaneous (SC) injection.[1]

INNOVATION AND/OR ADVANTAGES

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.[3] Setmelanotide has been shown to substantially reduce hyperphagia and body weight and offers a treatment for obesity in BBS and AS patients.[5,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Setmelanotide was granted EU Orphan Drug Status for BBS in August 2019.[7] It was also awarded EMA PRIME Designation for Rare Genetic Disorders of Obesity in June 2018.[8] Setmelanotide does not currently have Marketing Authorisation in the EU/UK.

Setmelanotide is currently in phase II/III trials for hypothalamic obesity and for rare genetic disorders of obesity.[9]

PATIENT GROUP

DISEASE BACKGROUND

BBS is a genetic condition that impacts multiple body systems inherited in an autosomal recessive pattern.[10] BBS can be caused by mutations in more than 20 different genes. There is no clear link between the different mutations identified and disease severity, but some trends have emerged.

The cardinal features of BBS are truncal obesity, intellectual impairment, renal anomalies, polydactyly, retinal degeneration and hypogenitalism. Weight is usually normal at birth, but weight gain is quickly evident through the first year of life in as many as 90% of people with BBS. Diabetes mellitus (specifically, type II diabetes, non-insulin dependent) has been

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estimated to affect up to 45% of patients with BBS. Weight management problems may further complicate issues with the heart and blood vessels seen in patients with BBS.[10]

AS is a rare complex genetic disorder that is associated with a wide variety of symptoms affecting multiple organ systems of the body inherited as an autosomal recessive trait.[11] AS is caused by mutations in the *ALMS1* gene. The *ALMS1* gene contains instructions for creating (encoding) a specific protein known as ALMS1. The role and function of this protein in the body is not fully understood, but believed to be involved in ciliary function, cell cycle control and intracellular transport. The ALMS1 protein is expressed in all organ tissues of the body.

The disorder is generally characterised by vision and hearing abnormalities, and obesity in childhood, insulin resistance, diabetes mellitus, dilated cardiomyopathy and slowly progressive renal dysfunction, potentially leading to renal failure. Birth weight is normal in infants with AS, but excessive eating beyond the normal need to satisfy hunger (hyperphagia) and rapid weight gain may occur during the first year of life. Some affected children develop childhood truncal obesity. As affected individuals age, some may see their body weight fall, often regaining normal or slightly above-average weight for their size.[11]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence for BBS in Europe is estimated at 0.7 per 100,000 and 0.5 for prevalence at birth.[12] It affects around 1 in 100,000 babies born.[13] It is estimated that there are around 560 affected individuals in the UK. There are no estimates on mortality, however, it is thought to depend on severity of symptoms and how well they are managed.

There are 950 reported cases of AS worldwide.[12] Alström Syndrome UK know of about 80 families in the UK who are affected but they estimate this figure is an underestimate.[14] AS affects males and females in equal numbers.[11] The exact incidence is unknown. Estimates have ranged from 1 in 10,000 to less than 1 in 1,000,000 individuals in the general population. Because some cases of AS may go unrecognised or misdiagnosed, the disorder may be under-diagnosed, making it difficult to determine its true frequency in the general population. AS occurs with greater frequency in ethnically isolated communities.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for BBS. The primary treatment goal for patients with BBS involves treating the specific symptoms affecting each individual. Early intervention for anticipated problems can ensure that people with BBS reach their greatest potential. As many body systems are involved, care often requires the coordinated effort of a team of specialists.[10]

There is no specific treatment for individuals with AS. Treatment is directed toward the specific symptoms that are apparent in each individual. Treatment will require the coordinated efforts of a team of specialists. Paediatricians, cardiologists, specialists who assess and treat hearing problems (audiologists), specialists who assess and treat vision problems (ophthalmologists), specialists who deal with the system of glands that secrete hormones into the bloodstream (endocrinologists), specialists who assess and treat skeletal problems (orthopaedists), and other healthcare professionals may need to systematically and comprehensively plan a child's treatment.[11]

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CURRENT TREATMENT OPTIONS

There are currently no pharmacological treatments licensed for the treatment of BBS or AS.

PLACE OF TECHNOLOGY

If licensed, setmelanotide will provide a first-line treatment for patients with obesity and hyperphagia due to BBS and AS.

CLINICAL TRIAL INFORMATION

Trial	NCT03746522; A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alström Syndrome (AS) Patients With Moderate to Severe Obesity **Phase III – active, not recruiting** **Location(s):** US, Canada, EU countries (incl UK) and Puerto Rico **Primary completion date:** December 2020
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N = 30; 6 years and older; BBS or AS diagnosis; obese
Intervention(s)	3mg setmelanotide (SC injection) - daily
Comparator(s)	Matched placebo
Outcome(s)	Effect of setmelanotide [time frame: 52 weeks]: The proportion of patients (greater than or equal to 12 years of age at baseline) who achieve a greater than or equal to 10% reduction from baseline in body weight (i.e., are 'responders') after ~52 weeks of treatment with setmelanotide.
Results (efficacy)	• 11 of 31 or 34.5% of participants achieved the primary endpoint of at least 10% reduction in body weight from baseline at approximately 52 weeks of therapy (p=0.0024); 11 of 28 patients with BBS achieved 10% reduction in body weight; 0 of 3 patients with AS achieved 10% reduction in body weight. • Mean reduction from baseline in body weight was -6.2% (p<0.0001); • Mean reduction from baseline in most hunger rating was -30.8% (p<0.0001); • 60.2% of participants achieved at least 25% reduction in most hunger scores from baseline at approximately 52 weeks of therapy (p<0.0001).[6]
Results (safety)	• Treatment-emergent adverse events (TEAEs) included mild injection site reactions and nausea with infrequent vomiting; • There were no serious adverse events (SAEs) related to treatment with setmelanotide; • Eight patients discontinued from study drug treatment during the trial, five due to adverse effects (one on placebo at the time), and three for other reasons (one on placebo at the time).[6]

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ESTIMATED COST

The cost of setmelanotide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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 Alström Syndrome service (All Ages). A17/S(HSS)e.

OTHER GUIDANCE

- No relevant guidance identified.

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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