Highly Specialised Technology

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Rhythm Pharmaceuticals
2. **Company summary of information for patients (SIP)** from Rhythm Pharmaceuticals
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Bardet-Biedl Syndrome UK
   b. British Obesity and Metabolic Surgery Society (BOMSS)
5. **External Assessment Report** prepared by Bristol Technology Assessment Group
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7. **Technical engagement response from company**
8. **External Assessment Report critique of company response to technical engagement** prepared by Bristol Technology Assessment Group
9. **External Assessment Report** addendum prepared by Bristol Technology Assessment Group
10. **Expert personal perspectives from:**
    a. Elizabeth Forsythe, Consultant in Clinical Genetics – clinical expert, nominated by Rhythm Pharmaceuticals
    b. Dimitri Pournaras, Consultant Bariatric and Metabolic Surgeon – clinical expert, nominated by British Obesity & Metabolic Surgery Society

c. Danielle Thomas – patient expert, nominated by Bardet-Biedl Syndrome UK
d. Angela Scudder – patient expert, nominated by Bardet-Biedl Syndrome UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Highly specialised technology evaluation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome ID3947

Document B

Company evidence submission

January, 2023

File name	Version	Contains confidential information	Date
ID3947 Setmelanotide BBS HST Company submission [no ACIC]v4	1.4	No	7th July 2023

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Executive summary

IMCIVREE (setmelanotide) is authorised for the treatment of obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children aged ≥6 years, however this submission is for a subpopulation of BBS patients who are classified as having severe hyperphagia and obesity. Severe hyperphagia is caused by impairment of the MC4R pathway which leads to overwhelming, heightened, and relentless hunger that mimics feelings of starvation and results in excessive food consumption and a preoccupation with food that interferes with a patient's ability to function in daily life. The result of severe hyperphagia is obesity, which affects 72% - 92% of patients with BBS (Forsythe 2018); the majority being obese by the age of 5 years (Pomeroy 2021). Early onset obesity is associated with increased mortality compared to the general population. A recent Swedish study demonstrated that individuals who were obese in childhood had a 3-times higher risk of mortality in early adulthood compared with a population-based comparison group (Lindberg 2020). Treating hyperphagia and obesity early may therefore reduce the associated comorbidities experienced by these patients, indirectly improving mortality.

Setmelanotide exerts its therapeutic effect by activating the MC4R pathway to reduce hyperphagia and subsequently reduce weight and BMI. In clinical trials of setmelanotide hunger reductions occurred in the first 14 weeks of treatment and were maintained throughout 52 weeks of treatment. Setmelanotide was also shown to be effective in inducing clinically meaningful reductions in body weight and BMI/BMI-Z score over 52 weeks of treatment:

- At 14 weeks patients of all ages treated with setmelanotide saw a mean decrease in hunger score of [redacted]% compared with [redacted]% for those receiving placebo.
- At 52 weeks mean % change in maximal hunger in patients treated with setmelanotide was -30.9% (p = 0.0001)
- Over 52 weeks of treatment with setmelanotide, 47% of patients with BBS aged ≥18 years of age achieved a ≥10% reduction in body weight from the active-treatment baseline, which was statistically significant (p=0.0003) compared with a historical control rate of 10%.
- In patients < 18 years of age, 86% achieved a ≥0.2 reduction from baseline in BMI Z-score over 52 weeks (95% CI 57.2, 98.2).

A cost-effectiveness analysis was carried out comparing setmelanotide plus best supportive care (defined as diet and exercise advice) with best supportive care alone. The base case considered data from the paediatric population as in future the majority of patients will be diagnosed and treated as children, however, patients who are currently adults can also benefit from setmelanotide and reimbursement is sought for both adult and paediatric patients. The base-case incremental cost-effectiveness ratio is £191,759/QALY with Commercial in confidence data removed total undiscounted quality-adjusted life years. The modelled benefit in overall survival is Commercial in confidence data removed years and Commercial in confidence data removed incremental quality adjusted life years.

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation. IMCIVREE (setmelanotide) is authorised for the treatment of obesity and control of hunger associated with genetically-confirmed Bardet-Biedl syndrome (BBS) in adults and children aged ≥6 years, however this submission is for a subpopulation of BBS patients who are classified as having severe hyperphagia. Severe hyperphagia is defined as overwhelming, heightened, and relentless hunger that mimics feelings of starvation and results in excessive food consumption and a preoccupation with food that interferes with a patient's ability to function in daily life. This position is narrower than the marketing authorisation because:

- This population optimises the cost effectiveness of setmelanotide because patients with severe hyperphagia experience significantly greater impact on their quality of life than those with mild or moderate hyperphagia.
- This population therefore reflects where setmelanotide provides the most clinical benefit.

The decision problem addressed by this submission is presented in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged ≥6 years with obesity and hyperphagia with BBS and the following obesity markers: • People aged ≥18: body mass index (BMI) of ≥30 kg/m^2 • People aged ≤17: weight of ≥97th percentile for age on growth chart assessment.	People aged ≥6 years with obesity and severe hyperphagia with BBS and the following obesity markers: • People aged ≥18: BMI of ≥30 kg/m^2 • People aged ≤17: weight of ≥97th percentile for age on growth chart assessment.	As specified in Section B.1.1
Intervention	Setmelanotide	Setmelanotide in combination with diet and exercise advice	Setmelanotide is not expected to replace diet and exercise advice for treatment of obese patients with BBS, rather it is expected to improve the impact of these interventions
Comparator(s)	• Established clinical management without setmelanotide (including a reduced calorie diet and increased physical activity) • Bariatric surgery	• Established clinical management without setmelanotide (including a reduced calorie diet and increased physical activity)	Bariatric surgery is not recommended for rare genetic disease of obesity (RGDO) patients and does not address the genetic impairment and resulting insatiable hunger. It is also not a suitable treatment option for patients with cognitive impairment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	Outcome measures to be considered: • BMI and BMI Z-score • Weight loss • Percent body fat • Waist circumference • Hunger • Incidence of type 2 diabetes (T2DM) • Cardiovascular events • Mortality • Co-morbidities associated with early onset severe obesity including cancer • Adverse effects of treatment • Health-related quality of life (HRQoL) for patients and carers	Outcome measures to be considered: • BMI and BMI Z-score • Weight loss • Percent body fat • Waist circumference • Hunger • Incidence of T2DM • Cardiovascular events • Mortality • Mortality effect associated with early onset severe obesity • Adverse effects of treatment • HRQoL for patients and carers	
Economic analysis		The model does not use EQ5D data for quality of life, instead, hyperphagia quality of life multipliers from a vignette study (Appendix O) are used	EQ5D was not deemed sufficiently sensitive to capture the impact of hyperphagia on quality of life
Subgroups to be considered	None specified	Paediatric BBS patients with severe hyperphagia Adult BBS patients with severe hyperphagia	Differences in study outcome are seen between adult and paediatric subgroups. Though the submission presents subgroup analyses for paediatric and adult patients, approval is sought for patients of all ages

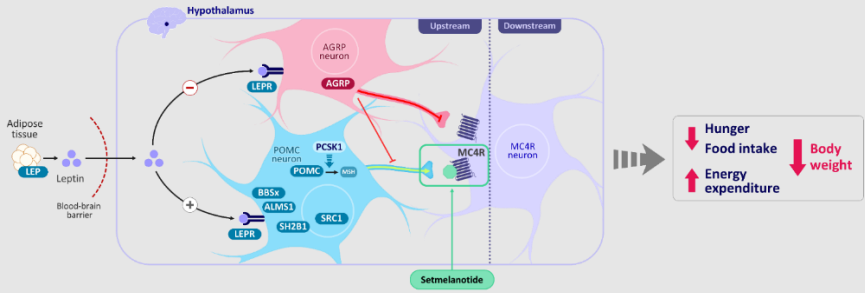
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	The base case cost-effectiveness analysis presented in this submission utilises clinical data from the paediatric population. In the future setmelanotide will be available to all BBS patients during childhood and prevent them from both overeating and developing bad eating habits that contribute to the progression toward becoming obese. In adults with BBS, the weight reductions seen were of smaller magnitude than those in paediatric patients. It is thought that this may be due to the establishment of bad eating habits that have become ingrained over a lifetime. Rhythm believes it is unethical to deny treatment to adults, who can still benefit from the reduction in hyperphagia but might see less weight reduction than children. Rhythm therefore seeks approval for both adults and children with BBS.		

B.1.2 Description of the technology being evaluated

Appendix C includes the summary of product characteristics and the UK public assessment report for IMCIVREE.

The technology being evaluated in this submission is described in Table 2.

Table 2 The technology being evaluated

UK approved name and brand name	UK approved name: Setmelanotide Brand name: IMCIVREE®
Mechanism of action	The melanocortin 4 receptor (MC4R pathway, Figure 1) is responsible for hunger and energy expenditure. Thus, defects in the pathway lead to increased food intake and body weight. It is believed that this pathway is responsible for the hyperphagia and obesity observed in BBS patients (Pomeroy 2021). **Figure 1 The hypothalamic MC4R pathway indicating some potential molecular defects upstream of the receptor**  AGRP, agouti-related peptide; ALMS1, Alström syndrome protein 1; BBSx, BBS-associated genes; LEP, leptin hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin; SH2B1, Src homology 2B adaptor protein 1; SRC1, steroid receptor coactivator-1. IMCIVREE is an MC4R agonist that retains the specificity and functionality of naturally occurring α-melanocyte stimulating hormone, the natural MC4R ligand. IMCIVREE has the potential to restore lost signalling activity in the MC4R pathway by compensating for defects upstream of the receptor and directly activating MC4R neurons in the hypothalamus. IMCIVREE has potential to act as a replacement therapy to re-establish a healthy appetite and energy expenditure and thus aid body weight regulation.
Marketing authorisation/CE mark status	The marketing authorisation for the indication in scope for this submission is treatment of obesity and control of hunger associated with genetically-confirmed BBS in adults and children aged ≥6 years. MHRA approval was granted on 17th November 2022.

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	IMCIVREE is indicated for the treatment of obesity and control of hunger in adults and children aged ≥6 years, associated with: genetically-confirmed BBS; loss-of-function biallelic biallelic leptin receptor (LEPR) deficiency; or pro-opiomelanocortin (POMC) including PCSK1 deficiency. Patients taking IMCIVREE with BBS and severe renal impairment must follow a separate dose titration schedule. IMCIVREE should not be administered to patients with BBS and end-stage renal disease. IMCIVREE should not be administered to patients with hepatic impairment.
Method of administration and dosage	IMCIVREE should be injected subcutaneously in the abdomen, thigh, or arm, using a different site each day. If a dose is missed, the once daily regimen should be resumed, as prescribed, with the next scheduled dose. IMCIVREE must not be administered intravenously or intramuscularly. IMCIVREE is a life-long treatment. It should be injected once daily, at the beginning of the day (to maximise hunger reduction during the awake period) without regard to the timing of meals. **Dose in adult and paediatric patients aged ≥16 years:** 2 mg once daily subcutaneous injection for 2 weeks. If well tolerated the dose can be increased to 3 mg once daily. If the 2 mg starting dose is not tolerated it can be reduced to 1 mg once daily. If 1 mg once daily is tolerated, dose titration can be resumed. After the starting dose, if a subsequent dose is not tolerated the dose should be reduced to the previous level. If the reduced dose is tolerated, dose titration can be continued. **Dose in paediatric patients (children aged 6 to <16 years):** 1 mg once daily subcutaneous injection for 1 week. If tolerated after 1 week, the dose can be increased to 2 mg once daily in the second week. If well tolerated, dose can be increased to 3 mg once daily from the third week. If the 1 mg starting dose is not tolerated, it should be reduce to 0.5 mg once daily. If the 0.5 mg once daily dose is tolerated, the dose can be increased to 1 mg once daily and titration continued.
Additional tests or investigations	IMCIVREE is indicated for genetically-confirmed BBS, therefore genetic confirmation the diagnosis must be obtained. Currently, all patients in England with a diagnosis of BBS are genotyped using a diagnostic gene panel (Forsythe 2018).
List price and average cost of a course of treatment	The NHS list price of IMCIVREE is £2376 per 10 mg/mL vial. IMCIVREE is a life-long therapy with an average annual cost per paediatric patient of Commercial in confidence data removed and an average annual cost per adult patient of Commercial in confidence data removed (assuming an average dose of Commercial in confidence data removed per day for paediatric patients and Commercial in confidence data removed per day for adults)
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) is in place for IMCIVREE's indication in POMC and LEPR deficiency. An updated PAS offering a Commercial in confidence data removed discount on the list price will apply to the BBS indication.

B.1.3 Health condition and position of the technology in the treatment pathway

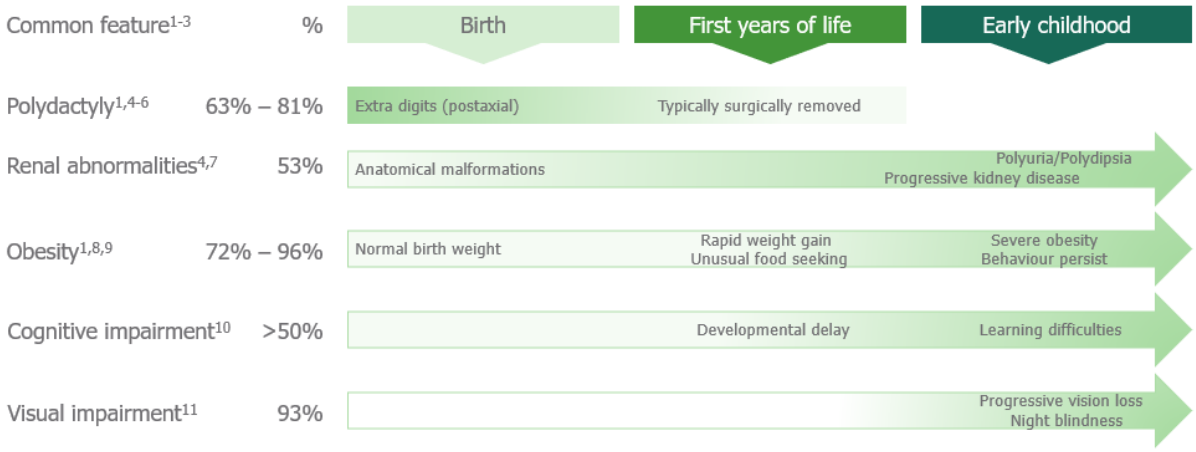
Overview of Bardet-Biedl syndrome

BBS is a rare autosomal recessive disease with an estimated prevalence of 1 in 100,000 in the UK (Great Ormond Street Hospital). It is a syndromic disease, which in many cases is characterised by hyperphagia (an overwhelming, heightened, and relentless hunger mimicking feelings of starvation) that leads to marked obesity. Other disease features that may be present include rod-cone dystrophy, postaxial polydactyly, cognitive impairment, hearing loss, speech deficit, hepatic fibrosis, genitourinary malformations, renal abnormalities, diabetes mellitus, hypertension and congenital heart disease (Bardet 1995, Biedl 1995, Beales 1999, Forsythe 2013, Forsythe 2015).

Obesity affects 72% to 92% of patients with BBS (Forsythe 2018). While most have normal birth weight, by 2 years of age it is estimated that >55% of children with BBS are overweight or obese and by the age of 5 years obesity rates exceed 90% (Pomeroy 2021). The mechanisms of obesity in BBS are believed to involve disruption of the hypothalamic leptin-melanocortin (MC4R) signalling pathway (Pomeroy 2021) responsible for regulation of appetite and satiety. Consequently, patients with BBS often have severe hyperphagia, a complex condition incorporating insatiable hunger (likened to feelings of starvation), longer time to reach satiety, shorter duration satiety, and distress if denied food (CARE BBS 2022). The insatiable hunger that is a component of hyperphagia leads to excess energy intake, resulting in continual weight gain throughout the patient's lifetime. Setmelanotide is an MC4R agonist and thus restores a BBS patient's ability to regulate appetite and satiety (the underlying cause of hyperphagia), thereby supporting weight loss.

Other symptoms of BBS include rod-cone dystrophy, which affects approximately 93% of patients (Forsythe 2018). It initially presents as night blindness at around the age of 7 to 8 years, and by the age of 16 years a significant proportion of BBS patients are legally blind (Forsythe 2015). Polydactyly is often present at birth, with other symptoms of BBS presenting variably and progressively throughout childhood (Figure 2).

Figure 2 Development of characteristic BBS symptoms



[1] Forsythe 2013, [2] Castro-Sanchez 2015, [3] Katsanis 2001, [4] Forsyth 2003, [5] Agrawal 2018, [6] Khan 2019, [7] Putoux 2012, [8] Pomeroy 2021, [9] Sherafat-Katzemzadeh 2013, [10] Beales 1999, [11] Weihbrecht 2017.

Life expectancy

There is currently no published evidence informing on the life expectancy of BBS patients. UK experts experienced in the treatment of BBS, estimate that patients have approximately a 10-year reduction in life expectancy compared with the general population; however, this will vary depending on the severity of the individual's symptoms. Renal failure is historically a major cause of mortality; a third of BBS patients develop renal failure and approximately 10% progress to end-stage renal failure requiring dialysis and/or transplant (UK for Bardet-Biedl syndrome service 2013); renal transplants have become increasingly effective and deaths from renal disease have decreased markedly in recent years (KOL opinion). Cardiovascular disease remains a significant issue for obese BBS patients (KOL opinion). It is widely accepted that increasing levels of obesity lead to higher mortality rates (Bhaskaran 2018), however there is now a growing appreciation that obesity that begins in childhood further increases mortality risk. A recent Swedish study demonstrated that individuals who were obese in childhood had a 3-times higher risk of mortality in early adulthood compared with a population-based comparison group (Lindberg 2020).

Diagnosis

Diagnosis of BBS relies on the presence of clinical symptoms, which can be categorised as primary or secondary features (Table 3). Obesity is one of six

potential primary features and results from uncontrollable hunger/hyperphagia. It is widely accepted that the presence of four primary features or three primary features and two secondary features is diagnostic of BBS. Whilst hyperphagia is not a diagnostic feature of BBS, it is increasingly accepted as an important disease feature that directly relates to obesity.

Table 3 Primary and secondary diagnostic features of BBS and their frequency (Forsythe 2018)

Primary features (frequency)	Secondary features (frequency)
• Rod-cone dystrophy (93%) • Polydactyly (63% to 81%) • Obesity (72% to 92%) • Genital anomalies (59% to 98%) • Renal anomalies (53%) • Learning difficulties (61%)	• Speech delay (54% to 81%) • Developmental delay (50% to 91%) • Diabetes mellitus (6% to 48%) • Dental anomalies (51%) • Congenital heart disease (7%) • Brachydactyly (46% to 100%)/syndactyly (8% to 95%) • Ataxia/poor coordination (40% to 86%) • Anosmia (60%)

Following clinical diagnosis, BBS is confirmed in approximately 80% of patients using genetic testing (Mujahid 2018). To date, 22 BBS-associated genes have been identified; BBS1 and BBS10 are most commonly involved and account for approximately 23% and 20% of cases respectively (Mujahid 2018). Patients with BBS1 mutations generally experience later onset visual deterioration and are less likely to develop renal disease than those with other BBS mutations (Forsythe 2018); however, the number and severity of symptoms is highly variable even between patients of the same genotype (Forsythe 2018).

Clinical pathway of care

Currently, patients in England with a diagnosis of BBS undergo genotyping using a diagnostic gene panel (Forsythe 2018).

Current treatment in BBS centres focuses on management of presenting features; patients, therefore, require input from many clinical services including ophthalmology, nephrology, urology, dietetics, endocrinology, clinical genetics and gynaecology (UK for Bardet-Biedl syndrome service 2013).

Patients in England with a diagnosis of BBS are assessed annually by a multidisciplinary team at one of four NHS trusts:

- Birmingham Children's Hospital NHS Foundation Trust
- Queen Elizabeth Hospital NHS Trust (Birmingham)
- Guys and St Thomas' NHS Foundation Trust (London)
- Great Ormond Street Hospital for Children NHS Foundation Trust (London)

These teams oversee the management of medical issues associated with BBS including delayed growth and puberty, hypogonadism, pituitary disorders, diabetes mellitus, obesity, lipid abnormalities, impaired renal and retinal function, cognitive impairment and behavioural issues (UK for Bardet-Biedl syndrome service 2013). For ongoing management, the BBS patient is referred back to their GP or another specialist (e.g. nephrologist) depending on their individual needs.

Current treatments

There are currently no licenced therapies for the treatment of obesity in patients with BBS. Rather, hyperphagia and obesity are managed symptomatically (mostly through lifestyle modification). Whilst diet and exercise advice can be effective in the short term, it does not address the underlying mechanism of impaired MC4R pathway signalling and the resulting severe hyperphagia that drives the patient to overeat. Weight management is particularly important for BBS patients as excess weight contributes to development of comorbidities such as T2DM, hypertension and metabolic syndrome (Forsythe 2018).

Impact of obesity and hyperphagia on BBS patient quality of life

Impact of obesity on quality of life

The impact of obesity on quality of life is well documented. Obese individuals are affected by numerous discriminations that impact on all dimensions of life (Sante Had 2011). They are often held responsible for their situation and can consequently feel stigmatised. For patients with BBS the situation can be especially difficult, as vision loss can prevent them participating in physical activities that they previously enjoyed, thereby confounding efforts to lose weight (BBS patient journey report).

Obese children are three times more likely than others to be victims of bullying, they have poorer school performance and find it more difficult to complete higher education (Estrada 2019). Patients with BBS have reported bullying and social isolation because of their obesity and condition (Qualitative interviews with setmelanotide trial participant report 2021):

“I felt very agitated and very sad a lot of the time…I just really didn’t have many friends, really even many friends to hang out with and…I don’t know. I just kind of felt alone in a sense” - BBS patient

“Because I gained so much weight, I did get bullied and that did bother me a lot.” – BBS patient

“I feel like it was just the judgment. She’s a good girl…They wouldn’t notice what a good-hearted person she was…They would notice how big she was” – BBS caregiver

Adults with obesity (BMI ≥30 kg/m^2) are at increased risk of developing major depressive disorder (Nigatu 2015) and some other mental disorders (low self-esteem, mood disorders, motivational disorders, eating problems, impaired body image and interpersonal communication issues; Djalalinia 2015). Adults with obesity are less likely to have a job, and when they do work they are more likely to be absent and be less productive (Estrada 2019). Being obese also puts people at increased risk of comorbidities such as hypertension, T2DM, non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnoea, all of which contribute to reduced quality of life (Narang 2012).

Impact of hyperphagia on quality of life

In addition to obesity, patients with BBS also have to deal with severe hyperphagia which can distract from activities of daily life. Studies that specifically address quality of life in patients with BBS, obesity and hyperphagia had not previously been conducted. Rhythm Pharmaceuticals, therefore, conducted a real-world study of 242 adult caregivers of patients with BBS, obesity and hyperphagia from the UK, US, Canada and Germany (CARE-BBS 2022).

Most caregivers reported numerous disruptive behaviours related to uncontrollable hunger occurring over the previous 24 hours. These included food negotiation during the day, eating extremely quickly, sneaking food, waking up and looking for food at night, and asking for more food just after finishing a meal or snack (CARE BBS 2022). Approximately 80% of caregivers also reported that uncontrollable hunger impacted on the patient's focus at school at least 'sometimes'; 81% of children had missed at least 1 day of school in the previous week due to BBS (CARE BBS 2022). The caregiver of a setmelanotide trial participant described the impact of hyperphagia on schooling (Qualitative interviews with setmelanotide trial participant report 2021):

"Because of the constant obsessive thoughts of food. I think it was hard for her to concentrate at school because she was always thinking about when they were going to eat." – BBS caregiver

In addition to the impact on schooling, other effects of hyperphagia included disruption of sleep, mood and emotions, leisure activities, and relationships with friends and family. When asked about the impact of hyperphagia over these 5 domains, 96.3% of caregivers reported that the patient they cared for had been affected either 'moderately' or 'a great deal' in at least one domain over the previous 7 days and 15.7% were affected either 'moderately' or 'a great deal' over all 5 domains (Table 4).

Table 4 Proportion of BBS patients impacted 'moderately' or 'a great deal' by hunger as assessed by the caregiver

Number of domains affected	N=242 carers
5 domains	38 (15.7%)
At least 4 domains	79 (32.6%)
At least 3 domains	134 (55.4%)
At least 2 domains	190 (78.5%)
At least 1 domain	233 (96.3%)
Not affected 'at all' or only 'a little' over all domains	9 (3.7%)

Impact of BBS on caregiver quality of life

Caring for a child with BBS is associated with a substantial caregiver burden. In early years, before a formal diagnosis, many experience anxiety over the health of their child as they sense that something is 'not right'; this is coupled with frustrations that their concerns are not taken seriously by healthcare professionals. In addition, comments about their child's weight can make parents feel blamed for over feeding and this further contributes to their anxieties (BBS patient journey report). Indeed, caregivers of BBS patients with obesity and hyperphagia reported using an average of 8 weight management approaches including healthy meal planning, counting/ restricting calorie and fat intake, tracking weight, counting/restricting carbohydrate intake, and limiting the availability of certain foods. Notably, 44.2% reported locking up food at night and 26.4% reported using fasting with their child (CARE BBS 2022). Managing the food intake of BBS patients also impacted on caregiver relationships with both their children and other family members and affected social participation:

"We didn't go places. And if you go to somebody's house, trying to keep them away from the chips and dip is so hard, it's easier to just not go"

"Lots of stress. Lots of worry for mom, for sure. Lots of guilt there too because you have to tell him 'no' a lot"

"And I tried very hard not to make it about the weight and issues with that. But it was very hard, because it's like, 'You shouldn't be eating that much'. It was starting to drive a wedge between her and I, and I was the bad guy."

"It affected my relationship with my husband. Because he is a lot better at saying no than I am…I would think he was being mean to her when really, he was doing what was best for her."

When asked specifically about the effect of the patient's hyperphagia on their own quality of life, caregivers reported the impact to be similar to that on their child; 90.9% of caregivers reported that their child's hyperphagia negatively affected them either 'moderately' or 'a great deal' in at least one domain (sleep, mood or emotions, work, leisure or recreational activities; Table 5).

Table 5 Proportion of BBS caregivers reporting being affected either 'moderately' or 'a great deal' by their child's hunger

Number of domains affected	N=242 carers
5 domains	38 (15.7%)
At least 4 domains	77 (31.8%)
At least 3 domains	130 (53.7%)
At least 2 domains	182 (75.2%)
At least 1 domain	220 (90.9%)
Not affected 'at all' or only 'a little' over all domains	22 (9.1%)

B.1.4 Equality considerations

It is not anticipated that this evaluation would: exclude any individuals protected by equality legislation from consideration for treatment; lead to a recommendation with a different impact for people protected by equality legislation than for the wider population; or lead to recommendations with an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Appendix D provides full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

Three clinical trials provide data on the clinical effectiveness of setmelanotide, comprising the pivotal Phase 3 Study RM-493-023 (NCT03746522), extension Study RM-493-022 (NCT03651765) and Phase 2 Study RM-493-014 (NCT03013543). The health-economic model uses baseline and response data from Study RM-493-023 and data from Study RM-493-022 to inform maintenance of efficacy. Data from RM-493-014 are not used in the model, as this was a Phase 2 study which was not designed to assess efficacy; however, patients from Study RM-493-014 were eligible to enter Study RM-493-022. As Study RM-493-014 data are not used in the health-economic model, the study is not described in this section but is summarised in Appendix N.

Publications providing clinical effectiveness data are presented in Table 6, Table 7 and Table 8. This submission includes data from both publications associated with key studies and the clinical study reports. In addition a systematic literature review (SLR) was conducted to identify any other data relating to the management of obesity and hyperphagia in BBS patients, as summarised in Appendix D.

No drug therapy is currently approved for the management of hyperphagia and obesity associated with BBS. The comparator used for modelling is standard management/best supportive care (BSC); no studies were identified by the SLR that compared setmelanotide directly with BSC.

Table 6 Clinical effectiveness evidence for pivotal Phase 3 Study RM-493-023 (NCT03746522)

	Haqq 2022	Argente 2021	Haws 2021a	Forsythe 2021	Haws 2021b
Title	Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome (AS): a multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial with an open-label period	A Phase 3 trial of setmelanotide in participants with Bardet-Biedl syndrome: placebo-controlled results	The efficacy and safety of open-label setmelanotide in Bardet-Biedl syndrome: a Phase 3 trial	Quality of life in patients with Bardet-Biedl syndrome in a setmelanotide Phase 3 trial	Efficacy and safety of the melanocortin-4 receptor agonist setmelanotide in obesity due to Bardet-Biedl syndrome: a Phase 3 trial
Study design	A randomised, double-blind, placebo-controlled, comparative study to evaluate the superiority of setmelanotide versus placebo over a period of 14 weeks, followed by an open-label treatment period of 52 weeks for patients who initially received placebo and of 38 weeks for those who initially received setmelanotide. All patients had received 52 weeks of setmelanotide treatment by the time of assessment of the primary endpoint.				
Population	Patients aged ≥6 years with a clinical diagnosis of BBS or AS who were obese (BMI ≥30 kg/m^2 for patients aged ≥16 years; weight ≥97th percentile for age and sex on growth chart assessment for patients aged 6 to 15 years).				

	Haqq 2022	Argente 2021	Haws 2021a	Forsythe 2021	Haws 2021b
	A total of 38 patients with BBS or AS were enrolled into the pivotal cohort and randomised to receive setmelamotide or placebo (19 patients in each treatment group, with in each group 16 having BBS and 3 having AS). Two patients in the placebo group discontinued the study during the 14-week randomised placebo-controlled period. The remaining 36 patients subsequently entered the 52-week open-label study period. Eight patients (21%) discontinued the study: 4 due to adverse events (AEs, 2 with BBS and 2 with AS), 2 patients (with BBS) were lost to follow-up, and 2 patients (1 each with BBS and AS) withdrew. A total of 28 patients (74%) completed the study.	A total of 32 patients with BBS were enrolled in the pivotal cohort (of whom 29 were aged ≥12 years) and received setmelamotide or placebo in the first 14 weeks of the study. Six patients discontinued the study: 3 due to AEs, 1 patient was lost to follow-up, and 2 patients withdrew. A total of 26 patients completed the study.	A total of 32 patients with BBS were enrolled in the pivotal cohort and 31 patients received open-label setmelamotide. Six patients discontinued the study: 3 due to AEs, 1 patient was lost to follow-up, and 2 patients withdrew. A total of 26 patients completed the study.	A total of 20 patients received open-label setmelamotide and provided baseline and Week 52 HRQoL data; 9 patients were aged 8 to 17 years. Ten patients were classified as not cognitively impaired, of whom 3 were aged 8 to 17 years.	A total of 32 patients with BBS were enrolled in the pivotal cohort and 31 patients received open-label setmelamotide (all 31 were aged ≥12 years). Fifteen patients were aged ≥18 years and 16 patients were aged <18 years.
Intervention	Setmelanotide 1.0 mg, 2.0 mg or 3.0 mg administered subcutaneously once daily				
Comparator	Matching placebo administered subcutaneously once daily over the first 14 weeks		None		
Supports application for marketing authorisation	Yes	Yes	Yes	Yes	Yes
Used in the economic model	Yes	Yes	Yes	Yes	Yes

	Haqq 2022	Argente 2021	Haws 2021a	Forsythe 2021	Haws 2021b
Rationale for non-use in the model	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Reported outcomes specified in the decision problem	• The proportion of patients aged ≥12 years who achieved at least10% bodyweight reduction from baseline after 52 weeks. • Mean percent change from baseline in bodyweight, weekly average of daily hunger score, and the proportion of patients who achieved at least 25% reduction in the weekly average of daily hunger score from baseline; all measured after 52 weeks • Mean percent change from baseline in bodyweight and weekly average of daily hunger score at Week 14 compared with placebo • In patients with BBS the proportion of: adults with at least 5% and 10% bodyweight reduction; paediatric and adolescent patients who achieved a clinically-relevant BMI Z-score reduction (at least 0.2 points and at least 0.3 points, respectively) • The proportion of patients achieving a reduction of at least 25% in the weekly average of daily hunger score from baseline Data used in the economic model were taken directly from clinical study reports.	Comparison of setmelanotide vs placebo in participants aged ≥12 years, in terms of change from baseline to 14 weeks in: • Body weight • BMI or BMI Z-score • Hunger score	Change from baseline to 52 weeks in: • BMI or BMI Z-score • Bodyweight • Hunger score	Change from baseline to 52 weeks in: • BMI or BMI Z-score • Hunger score	Change from baseline to 52 weeks in: • Body weight • BMI or BMI Z-score • Hunger score Considering patients aged ≥12 years, ≥18 years and <18 years

	Haqq 2022	Argente 2021	Haws 2021a	Forsythe 2021	Haws 2021b
All other reported outcomes	Within-patient change in total cholesterol, low-density lipoprotein cholesterol, triglycerides, body fat, and waist circumference after 52 weeks.	None	None	None	None

Table 7 Clinical effectiveness evidence for long-term extension Study RM-493-022 (NCT03651765)

	Argente 2022
Title	Long-term efficacy of setmelanotide in patients with Bardet-Biedl syndrome
Study design	Open-label extension trial of long-term setmelanotide treatment
Population	Patients aged ≥6 years who had completed a prior trial with setmelanotide and demonstrated clinical efficacy. Fifty-four patients with BBS enrolled in the study and received setmelamotide (28 patients aged <18 years, 26 patients aged ≥18 years). Four patients discontinued the study due to patient withdrawal (3 patients) or the occurrence of an AE (1 patient). Thirty-eight patients were receiving ongoing treatment at the time of analysis.
Intervention	Setmelanotide 1.0 mg, 2.0 mg or 3.0 mg administered subcutaneously once daily
Comparator	None
Supports application for marketing authorisation	Yes
Used in the economic model	Yes
Rationale for non-use in the model	Not applicable
Reported outcomes specified in the decision problem	Outcomes were assessed after ~2 years of setmelanotide treatment across the index and long-term extension trials and comprised: • Change in body weight measures relative to the index trial baseline, analysed for adult and paediatric subgroups • Change in BMI, BMI Z-score and percent of the BMI 95th percentile Data used in the economic model were taken directly from clinical study reports.
All other reported outcomes	None

Table 8 Clinical effectiveness evidence for Phase 2 Study RM-493-014 (NCT03013543)

	Haws 2020
Title	Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome
Study design	An open-label, single-arm, basket-design, Phase 2 pilot study assessing the effect of setmelanotide on obesity in patients with various rare genetic disorders of obesity over an initial dose titration/proof-of-concept phase of up to 12-weeks. Patients who demonstrated at least 5 kg weight loss at the end of 12 weeks continued into the 52-week extension phase.
Population	Patients aged ≥12 years with a confirmed diagnosis of a rare genetic disorder of obesity caused by a mutation that affects the function of the MC4 pathway and were obese (BMI ≥30 kg/m^2 for patients aged ≥18 years; weight ≥97th percentile for age and sex on growth chart assessment for patients aged 12 to 17 years). Ten patients with BBS enrolled in the study and received setmelamotide. Two patients discontinued during the dose titration/proof-of-concept phase, due to patient withdrawal (1 patient) or insufficient weight loss for entry into the extension phase (1 patient). Of the 8 patients who entered the 52-week extension phase, 7 patients completed the study.
Intervention	Setmelanotide 0.5 mg, 1.0 mg with dose titration in 0.5 mg increments every 2 weeks to a maximum of 3.0 mg, administered subcutaneously once daily
Comparator	None
Supports application for marketing authorisation	Yes
Used in the economic model	No
Rationale for non-use in the model	The trial was not designed as an efficacy study
Reported outcomes specified in the decision problem	• Percent change from baseline in bodyweight after 3, 6 and 12 months of treatment at the therapeutic dose • Daily hunger score, BMI, body fat mass, glucose-related variables, and waist circumference No data from this trial were included in the model.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

This section includes data from the clinical study reports for Study RM-493-023 (Phase 3 study) and Study RM-493-022 (open-label extension trial), which inform on the economic model. A summary of Study RM-493-014 is provided in Appendix N.

B.2.3.1 Trial methodology

Study RM-493-023

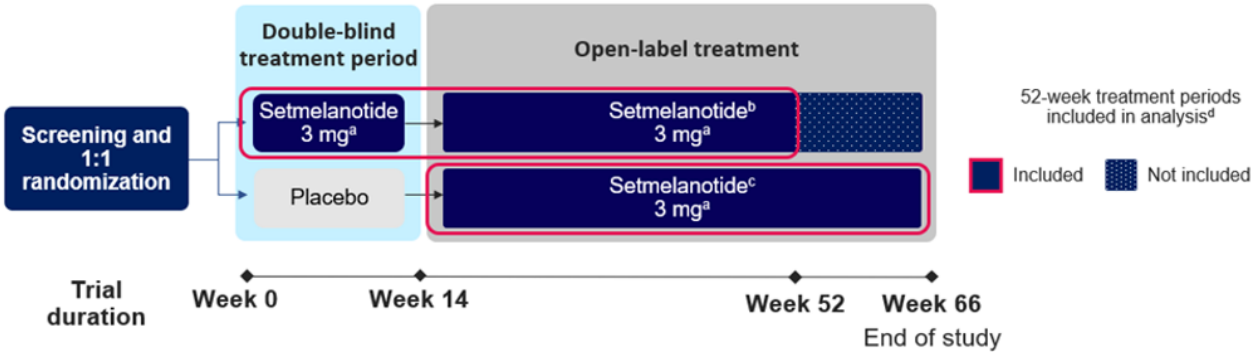
The main study providing data relating to the use of setmelanotide in patients with BBS is derived from Phase 3 pivotal Study RM-493-023. The study was a 14-week randomised controlled trial against placebo with an open-label extension period providing approximately 52 weeks of data. The trial was conducted in both AS and BBS patients, however AS was not included in the setmelanotide marketing authorisation and so this submission focusses on post-hoc analysis of data in BBS patients only.

Trial design

Study RM-493-023 had a 2-arm, parallel-group design, with three treatment periods (Figure 3):

- Period 1 was a 14-week, randomised, double-blind, placebo-controlled treatment period. Patients were randomised in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive setmelanotide or placebo once daily via subcutaneous injection.
- Period 2 was a 38-week open-label treatment period in which all patients received setmelanotide.
- Period 3 was a 14-week open-label treatment period in which all patients received setmelanotide. The purpose of this period was to allow patients who received placebo in period 1 to receive 52 weeks of treatment. Those who received setmelanotide in Period 1 continued to receive setmelanotide after assessment of the Week 52 primary endpoint.

Figure 3 Study RM-493-023 design schematic



[a] Dose escalation up to 3.0 mg based on age
[b] For patients who received ≥52 weeks of setmelanotide treatment by end of study, the analysis was performed at Week 52.
[c] A multiple imputation model was used to impute data for patients who received <52 weeks of setmelanotide at the primary analysis timepoint
[d] Efficacy outcomes were assessed at 52 weeks of active treatment for each group (i.e. Week 0 to 52 for the setmelanotide group and Week 14 to 66 for the group assigned to placebo during the double-blind treatment period)

The study aimed to test whether the proportion of patients (aged ≥12 years) treated for ~52 weeks who achieved a ≥10% reduction from baseline in body weight was greater with setmelanotide than with a historical control rate of 10%. This control rate was based on an analysis of data from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS). The CRIBBS is a longitudinal registry housed at the Marshfield clinic, Madison, WI. Body weight of BBS patients is collected approximately annually and over 400 1-year intervals assessing annual body weight changes are available. These data were used to provide input for the sample size/power calculations and to estimate the natural history (non-treatment) response rate for the primary efficacy endpoint. Data from CRIBBS suggest that over a 1-year period, only [redacted]% of patients aged >6 years lost more than 10% body weight. The power calculations assume a null historical control value of 10% of patients who meet the response criterion, which is expected to be a conservative estimate.

After completion of Study RM-493-023, patients could enter an open-label extension study (Study RM-493-022) and continue setmelanotide treatment.

During study RM-493-023, conduct was changed to permit enrolment of a cohort of supplemental patients to gain more experience with setmelanotide treatment given the ultra-rare nature of BBS. A protocol amendment issued after the pivotal cohort had fully enrolled specified that supplemental patients were considered as having

completed the study if they received at least 24 weeks of study treatment and could enter the extension study (RM-493-022) at this time. Therefore, only pivotal patient data were included in the primary endpoint at 52 weeks. However, both pivotal and supplemental patient data were included in 14-week placebo comparison endpoints.

Eligibility criteria

The trial included patients aged ≥6 years with a clinical diagnosis of BBS or AS, and obesity defined as BMI ≥97th percentile for age and sex on growth charts for those aged 6 to <16 years and ≥30 kg/m^2 for those aged ≥16 years. These ages were used because healthy BMI levels vary throughout adolescence, and it is more appropriate to express BMI in terms of percentiles. Historical data indicate that most patients aged ≥16 years have minimal additional growth in height and it was, therefore, deemed appropriate to use standard BMI measures of obesity in these patients. It was planned that the study would recruit approximately 30 patients (at least 20 with BBS and at least 6 with AS) into the initial cohort to be included in the pivotal analysis. Patients were treated in a tertiary care setting but could be recruited from primary, secondary, or tertiary healthcare.

Patients with BSS were to fulfil the following inclusion criteria:

1) Have a BBS clinical diagnosis as per Beales 1999 (with either 4 primary features or 3 primary and 2 secondary features).

Primary diagnostic criteria	
Rod cone dystrophy	Learning disabilities
Polydactyly	Hypogonadism in males
Obesity	Renal anomalies
Secondary diagnostic criteria	
Speech disorder/delay	Mild spasticity (especially lower limbs)
Strabismus/cataracts/astigmatism	Diabetes mellitus
Brachydactyly/syndactyly	Dental crowding/hypodontia/small roots/high arched palate
Developmental delay	Left ventricular hypertrophy/congenital heart disease
Polyuria/polydipsia (nephrogenic diabetes insipidus)	Hepatic fibrosis
Ataxia/poor coordination	

At least 90% of BBS patients were to have their diagnosis confirmed genetically.

2) Be ≥6 years of age. Approximately 4 patients with BBS aged ≤12 years were to be enrolled into the pivotal cohort, with no age restrictions relating to patient numbers enrolled after the initial cohort.
3) Be obese (BMI ≥30 kg/m^2 for patients aged ≥16 years or weight ≥97th percentile for age and sex on the growth chart for patients aged 6 to 16 years).
4) The participant and/or parent or guardian was to be able to communicate well, understand and comply with study requirements, and understand and sign written informed consent.
5) Female participants of child-bearing potential were to be confirmed as non-pregnant and agree to use contraception. Female participants of non-childbearing potential (surgically sterile post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; postmenopausal for at least 12 months confirmed by a follicle stimulating hormone level in the post-menopausal range; or failure to have progressed to Tanner Stage V; and/or failure to have achieved menarche) did not need to use contraception.
6) Male participants with female partners of childbearing potential were to use double-barrier contraception if they were sexually active during the study or within the 90 days following study participation. Male patients were not to donate sperm during and for the 90 days following participation in the study.

The following were reasons for exclusion from the study:

1) Recent (within 2 months) intensive diet and/or exercise regimen with or without use of weight-loss agents (including herbal medications) that resulted in >2% weight loss.
2) Use of any medication approved to treat obesity within 3 months of randomisation. A glucagon-like peptide-1 (GLP-1) receptor agonist could be used up to the dose approved for treatment of diabetes mellitus (e.g. liraglutide up to a daily dose of 1.8 mg) as long as: it was not prescribed to treat obesity; the dose had been stable for at least 3 months prior to randomisation; the patient had not experienced weight loss during the previous 3 months; the patient intended to keep the dose stable throughout the study.

3) Prior gastric bypass surgery resulting in durable >10% weight loss with no evidence of weight regain. Patients could be considered if surgery was not successful, resulted in <10% weight loss, or there was clear evidence of weight regain after an initial response. Patients with a history of bariatric surgery were to be approved by the Sponsor.
4) Diagnosis of schizophrenia or bipolar, personality or other psychiatric disorders that the investigator believed would significantly interfere with study compliance. Neurocognitive disorders affecting ability to consent were not disqualifying as long as an appropriate guardian could give consent.
5) In patients with no significant neurocognitive deficits: a Patient Health Questionnaire-9 (PHQ-9) score of ≥15; any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS); a lifetime history of a suicide attempt; or suicidal behaviour in the last month.
6) Current, clinically-significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound results. A patient with potentially clinically-significant disease was to be reviewed by the Sponsor.
7) Haemoglobin A1c (HbA1c) >9.0% at screening.
8) A history of significant liver disease or liver injury, or a current liver assessment due to abnormal liver tests for an aetiology other than NAFLD; aetiologies including non-alcoholic steatohepatitis (NASH), other hepatitis causes, or history of hepatic cirrhosis were exclusionary.
9) Moderate to severe renal dysfunction, defined as a glomerular filtration rate of <30 mL/minute.
10) History or close family history (parents or siblings) of skin cancer or melanoma (excluding non-invasive basal or squamous cell lesion), or a patient history of ocular-cutaneous albinism.
11) Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesions), determined during comprehensive skin evaluation at screening. Any lesions of concern identified were to be biopsied and confirmed as benign prior to enrolment.
12) Patient not suitable for the study in the opinion of the investigator.

13) Participation in a clinical study with an investigational drug/device within the 3 months prior to the first dosing day.
14) Previous enrolment in a setmelanotide clinical study or prior setmelanotide exposure.
15) Significant hypersensitivity to study drug.
16) Inability to comply with the injection regimen.
17) Enrolment of a first degree relative (e.g. parent, sibling) in the study within the previous 4 months, or currently in the double-blind part of the study.

Important changes to eligibility criteria that were implemented after the study had commenced included:

- Use of GLP-1 receptor agonists was permitted.
- Removal of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition disorders as an exclusion criteria: DSM-V was removed to broaden the exclusion to include any psychiatric disorders that the investigator thought would interfere with the study.
- Exclusion from the study of patients with haemoglobin A1c of >9.0% at Screening: Patients with uncontrolled diabetes are likely to adjust concomitant medications during the study, in a manner not allowed by the protocol. In addition, fluctuations in diabetes control may affect weight, thereby confounding the primary endpoint.
- Exclusion from the study of patients with prior participation in a setmelanotide study: given the double-blind nature of the study, treatment-naïve patients were considered appropriate for this study.
- Exclusion from the study of first-degree relatives who had been enrolled in the study within the previous 4 months: To maintain the blind, relatives were not to be enrolled in the blinded period at the same time.

Settings and location where data were collected

This study was conducted at 12 centres in the US, Canada, the UK, France, and Spain. Study centres comprised research centres and hospitals. Patients were recruited from primary, secondary, or tertiary healthcare.

Most patients enrolled into RM-493-023 were located at study sites in the US. Two patients were located at study centres in the United Kingdom (Table 9).

Table 9 Study site location for BBS patients enrolled in Study RM-493-023

Location	RM-493-023
USA	28
Canada	5
Spain	5
France	3
United Kingdom	2
Germany	1

Interventions

Patients were randomised to setmelanotide or matching placebo during the 14-week double-blind treatment period. Patients aged <16 years received a starting dose of 1.0 mg once daily which could be increased to 2.0 mg after 1 week and to 3.0 mg after 2 weeks based on safety/tolerability; patients aged ≥16 years received a starting dose of 2.0 mg once daily which could be increased to 3.0 mg after 1 week. After Week 14, patients entered the open-label treatment period and all received setmelanotide; all patients repeated the dose-escalation procedure to maintain the study blind.

Study drug doses were not to be adjusted after dose-escalation completed and there was to be no change in exercise or other supportive regimens.

Setmelanotide was administered as a daily subcutaneous injection by the patient/caregiver. On clinic days the dose was administered at the study site, with other doses administered by the patient/caregiver at home.

Concomitant medication

Medications approved to treat obesity were not allowed within 3 months of randomisation and were prohibited during the study.

GLP-1 receptor agonists were permitted up to the dose approved for diabetes mellitus treatment as long as (1) not prescribed for to treat obesity, (2) the dose had been stable for at least 3 months prior to randomisation, (3) the patient had not

experienced weight loss during the previous 3 months, and (4) the patient intended to keep the dose stable during the study.

Other medications that could theoretically cause weight loss were allowed as long as the patient (1) had used them at a stable dose for at least 3 months prior to randomisation, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable during the study.

All concomitant medications were to be used at a stable dose during the study, unless dose change was necessary to treat an AE.

During the study, conduct was changed to permit the use of GLP-1 receptor agonists and remove the prohibition on use of anorectic agents or drugs with anorexia as a non-rare side effect. This was due to feedback from study sites that prompted further clarification on permitted medications.

Outcomes

The primary efficacy endpoint was the proportion of patients aged ≥12 years who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment. Weight was measured in triplicate and mean weight calculated at the study visit and used for analysis.

Key secondary efficacy endpoints comprised:

- Mean percent change in body weight from baseline in patients aged ≥12 years after ~52 weeks of treatment.
- Percent change in daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment. Hunger was assessed in patients aged ≥12 years who were not considered cognitively impaired, using the Daily Hunger Questionnaire. In patients assessed as cognitively impaired, hunger was assessed using the Prader-Willi syndrome Food Problem Diary (PWS-FPD), a caregiver-completed questionnaire designed to assess behaviours associated with hunger; the PWS-FPD was used as there is no validated hunger assessment specifically for patients with BBS and cognitive impairment. Two global hunger questions were used to assess the current static hunger state comprising: the patient global impression of severity (PGIS) and the patient global impression of change (PGIC); the PGIS was administered at baseline and

both PGIS and PGIC were administered at each subsequent visit. Three aspects of hunger (average hunger in the last 24 hours, most/worst hunger in the last 24 hours, and morning hunger) were assessed daily using a numeric rating score for each from 0 to 10, with 0 = not hungry at all and 10 = hungriest possible.

- The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks of treatment.

Secondary efficacy analyses for the 14-week, placebo-controlled period comprised:

- Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment.
- Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment.

Exploratory endpoints included:

- The proportion of patients of any age who achieved a ≥10% reduction from baseline in body weight after ~52 weeks of treatment.
- The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% at 14 weeks.
- Composite response rate, defined as patients who achieved either a ≥10% reduction in body weight or a ≥25% improvement in the weekly average of daily hunger score at ~52 weeks of treatment.
- The proportion of patients aged ≥12 years who met categorical thresholds of 5%, 15%, 20%, 25%, 30%, 35%, and 40% weight loss from baseline after ~52 weeks of treatment.
- The proportion of patients aged ≥12 years who achieved a ≥10% reduction from baseline in body weight or a ≥15% reduction in BMI after ~52 weeks of treatment.
- Change and percent change in BMI Z-score from baseline after ~52 weeks of treatment in paediatric patients by age group (6-11 years and/or 6-16 years).
- Descriptive statistics for change and percent change from baseline in waist circumference after ~52 weeks of treatment

- Descriptive statistics for change and percent change from baseline in total body mass (including body fat, non-bone lean mass, and bone density) after ~52 weeks of treatment.
- Summary statistics for global hunger response by active-treatment visit based on the questions: “Overall, how would you rate the hunger you experience now?” for patients aged ≥12 years; and “How hungry is your child acting now?” for patients aged <12 years.
- Descriptive statistics for change and percent change from baseline in PWS-FPD and the Prader-Willi syndrome Sensory Experiences Questionnaire (PWS-SEQ) after ~14 weeks of treatment for cognitively impaired patients aged ≥12 years after ~52 weeks of treatment.
- Descriptive statistics for change and percent change from baseline in measures of insulin sensitivity/resistance (fasting glucose, HbA1c, oral glucose tolerance test, and insulin) after ~52 weeks of treatment.
- Descriptive statistics for change and percent change from baseline in fasting lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) after ~52 weeks of treatment.
- SF-36 health survey version 2 (SF-36V2) and SF-10 health survey for children domain and composite summary score and change from baseline after ~52 weeks of treatment.
- Quality of life after 14 and ~52 weeks of treatment, as measured by the Pediatric Quality of Life Inventory (PedsQL) or Impact of Weight on Quality of Life-Lite (IWQOL-Lite), age-dependent, and EQ-5D actual scores and change from baseline.

Evaluation of setmelanotide safety and tolerability was assessed throughout the study.

During the study, following feedback from the US Food and Drug Administration, a key secondary objective to assess the effect of setmelanotide on the proportion of patients achieving ≥10% body weight reduction after ~52 weeks and another secondary objective to assess the effect of setmelanotide on the proportion of patients achieving a ≥25% improvement in hunger score by Week 14 were removed.

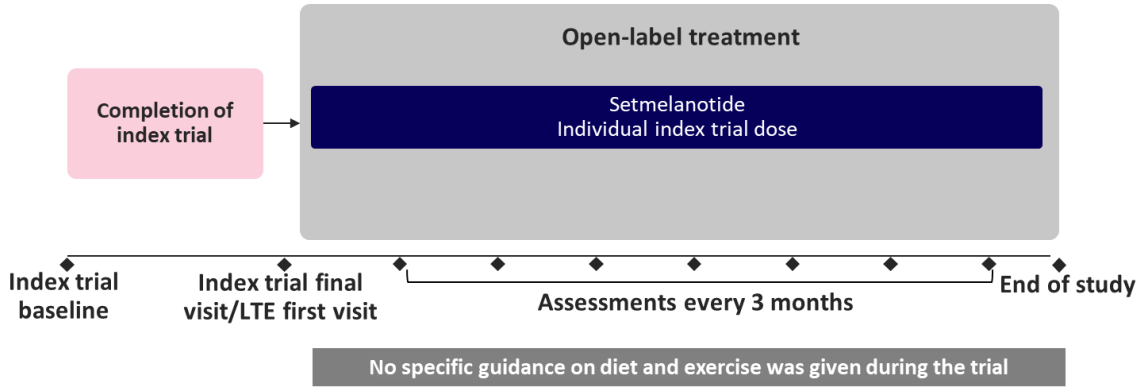
In addition, an exploratory endpoint to assess the proportion of patients with an improvement in daily hunger score was added.

Study RM-493-022

Trial design

Study RM-493-022 is an ongoing, Phase 3, open-label extension study to provide up to 2 years' additional setmelanotide treatment for patients who completed a prior index study for genetic obesity disorders with a mutation upstream of the MC4 receptor in the melanocortin-leptin pathway. The design of Study RM-493-022 is summarised in Figure 4. This submission presents data from BBS patients, all of whom were previously enrolled in Study RM-493-023 or RM-493-014. It also focuses on a post-hoc analysis of patients who were considered to be responders (patients aged ≥18 years achieving ≥10% weight reduction or patients aged <18 years achieving a ≥0.3 BMI Z-score reduction) after 1 year of setmelanotide treatment in their index trial. The rationale for this is that patients who do not respond to setmelanotide in clinical practice will discontinue treatment.

Figure 4 Study RM-493-022 design schematic



Eligibility criteria

The study was to recruit setmelanotide patients from trials across a range of disease indications with a genetic obesity component. It was initially planned that the study would recruit up to 100 patients across all disease indications. As far as was possible, qualifying patients were to be enrolled immediately on completion of their index study to avoid an interruption in setmelanotide treatment.

Patients were to fulfil the following inclusion criteria:

1) Be ≥6 years of age and have completed participation and demonstrated adequate safety in a previous setmelanotide study for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway.
2) The participant and/or parent or guardian was able to communicate well with the investigator, understand and comply with study requirements, and to understand and sign written informed consent/assent.
3) Female participants of child-bearing potential were to agree to use contraception. Female participants of non-childbearing potential (surgically sterile, postmenopausal for at least 12 months, or with delayed pubertal development and not having achieved menarche) did not require contraception. Male participants with female partners of childbearing potential were to agree to use a double barrier method if sexually active during the study. Male patients were not to donate sperm during and for 90 days following participation in the study.

The following were reasons for exclusion from the study:

1) Current, clinically-significant disease severe enough to interfere with the study and/or confound the results.
2) Pregnancy and/or breastfeeding.
3) Diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental Disorders, Third Edition disorders that the investigator believed would interfere significantly with study compliance.
4) A PHQ-9 score of ≥15.
5) Any suicidal ideation of type 4 or 5 on the C-SSRS. Any lifetime history of a suicide attempt, or any suicidal behaviour in the previous month.
6) Current, severe, stable, restrictive or obstructive lung disease as a consequence of extreme obesity; evidence of significant heart failure (New York Heart Association Class 3 or greater); or oncologic disease severe enough to interfere with the study and/or confound the results.
7) History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver tests for an aetiology other than non-alcoholic fatty liver.

Any other underlying aetiology, including diagnosed NASH, other causes of hepatitis, or history of hepatic cirrhosis were exclusionary.

8) History or presence of impaired renal function.
9) History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism.
10) Significant dermatological findings relating to melanoma or pre-melanoma skin lesions.
11) The patient was, in the opinion of the study investigator, not suitable to participate in the study.
12) Significant hypersensitivity to the study drug.
13) Inability to comply with the injection regimen.
14) Patients who had been placed in an institution through an official or court order, or who were dependent on the sponsor, investigator or study site.

Settings and locations where data were collected

This multicentre study was conducted at 5 study centres in the US, Canada, Spain, France and the UK. Study centres comprised research centres and hospitals. Most patients enrolled into RM-493-022 were located at study sites in the US. Two patients were located at study sites in the United Kingdom (Table 10).

Table 10 Study site location for BBS patients enrolled in Study RM-493-022

Location	RM-493-022
USA	29
Canada	4
Spain	3
France	4
United Kingdom	2

Interventions

Patients continued taking the same setmelanotide dose (0.5 mg to 3.0 mg once daily) as administered on completion of their index study. Dose level changes were allowed at any time, based on safety or efficacy findings, with dose adjustments made in increments of 0.5 mg. Downward titration was allowed after discussion with the Sponsor. If dose increase was deemed necessary, the patient was to remain

under observation for approximately 3 hours after administration of the first higher dose.

Setmelanotide was administered as a daily subcutaneous injection by the patient/caregiver. On clinic days the dose was administered at the study site, with other doses administered by the patient/caregiver at home.

The maximum dose permitted differed between countries, based on competent authority recommendations. At the time the study was conducted the US and Canada had approved a maximum daily dose of 3.0 mg, while Germany had approved a maximum daily dose of 2.5 mg.

Concomitant medication

The aim was to allow as many potential patients as possible with these ultra-rare indications to participate in the study. Therefore, patients were allowed to continue with other chronic concomitant medications such as: growth hormone, contraceptives, hormone replacement therapy, anti-hypertensives, statins and other lipid-lowering therapies, and thyroxine or other thyroid supplements. Other medications commonly used in obese patients could also be continued including endocrine therapies (e.g., oestrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetes therapies) and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications). These medications were permitted, on consultation with the Sponsor, if the patient was taking a stable dose.

Medications that could impact on efficacy assessments, such as anorectic agents or drugs with anorexia as a non-rare side effect were prohibited; low-threshold drugs (e.g. anticonvulsants, digoxin, Coumadin) were not permitted.

Outcomes

The primary endpoint was to characterise the safety and tolerability of setmelanotide, assessed by the frequency and severity of AEs; changes in physical examination, electrocardiogram (ECG), vital sign, and laboratory evaluations; and the occurrence of injection site reactions. Assessment of safety used the same parameters as the index studies, to allow all patients (regardless of the disease under study) to be assessed in a single extension study. During the course of the study, conduct was

changed by a protocol amendment that allowed patients experiencing an AE or abnormal laboratory value the opportunity for rechallenge with vehicle control (placebo) or lower setmelanotide doses to gain further information on relatedness to study drug.

No secondary endpoints were specified for this study. Exploratory endpoints included:

- The proportion of patients with ≥10% weight loss; this endpoint was included to replace yearly mean percent change from baseline in body weight during study conduct.
- Hunger, assessed at each visit using a daily questionnaire and 2 global questions.
- Yearly body composition including total body weight loss, fat loss, and non-bone lean mass.
- Waist circumference, measured according to United States National Heart Lung and Blood Institute criteria.
- Potential improvements in lipid levels (fasting cholesterol and triglycerides).
- Quality of life was assessed yearly using the validated self-reporting instruments IWQOL-Lite (specific for obesity) for participants aged ≥18 years and the measurement model for the PedsQL for participants aged <18 years. The validated self-reporting instruments SF-36 or SF-10 were used to measure functional health and well-being. Use of SF-10 and PedsQL was included during study conduct, when the potential to recruit paediatric patients into the study was specified.
- Biomarkers predictive of a setmelanotide response and/or rate of weight loss change could be evaluated using metabolic biomarkers. Such pharmacodynamic markers could include neuroendocrine and endocrine indicators of energy metabolism (e.g. ghrelin, leptin, insulin, orexin, and oxytocin, peptide YY, glucagon-like peptide-1, melanocyte stimulating hormone, pro-insulin, adrenocorticotropic hormone, brain-derived neurotrophic factor) or anti-inflammatory markers such as high-sensitivity C reactive protein.

- C-SSRS and PHQ-9 scores; use of C-SSRS was included during study conduct, when the potential to recruit paediatric patients into the study was specified.

Following study completion a post-hoc analysis was carried out, which included only BBS patients who were considered responders in their index trial i.e. those who had achieved ≥10% reduction in body weight (adults ≥18 years) or ≥0.3 points in BMI Z-score (paediatrics <18 years). This was considered reflective of future clinical practice, where patients would need to demonstrate clinically-significant weight loss in order to continue treatment with setmelanotide in the long-term.

B.2.3.2 Comparative summary of trial methodology

The design and methodology of Studies RM-493-023 and RM-493-022 are summarised in Table 11.

Table 11 Comparative summary of trial methodology for Studies RM-493-023 and RM-493-022

Trial number	Study RM-493-023	Study RM-493-022
Location	The US, Canada, UK, France, and Spain	The US, Canada, UK, France, and Spain
Design	A Phase 3 study to confirm the long-term efficacy and safety of setmelanotide treatment in patients with BBS or AS. The study comprised 3 periods: • Period 1 was a 14-week, randomised, double-blind, placebo-controlled treatment period. • Period 2 was a 38-week open-label treatment period in which all patients received setmelanotide. • Period 3 was a 14-week open-label treatment period in which patients who received setmelanotide in Period 1 continued to receive setmelanotide after assessment of the Week 52 primary endpoint. All patients had received ~52 weeks of setmelanotide treatment by the time of assessment of the primary endpoint.	An open-label extension study of up to an additional 2 years of treatment with setmelanotide for patients who had completed a prior setmelanotide study.
Eligibility criteria	Patients were to be ≥6 years of age, have a BBS clinical diagnosis and be obese.	Patients who had completed all critical study evaluations in a previous setmelanotide trial and would benefit from continued setmelanotide treatment.
Settings where data were collected	Study centres comprised research centres and hospitals.	Study centres comprised research centres and hospitals.
Trial drugs	Setmelanotide 1.0 mg, 2.0 mg and 3.0 mg or matching placebo (32 patients with BBS in the pivotal set and 12 in the supplemental set; 28 patients with BBS aged ≥12 years in the pivotal set and 7 in the supplemental set).	Setmelanotide was administered at the same dose (0.5 mg to 3.0 mg) as administered at the end of participation in the index study (42 patients with BBS).

Trial number	Study RM-493-023	Study RM-493-022
Permitted and disallowed concomitant medication	Medications approved to treat obesity were prohibited during the study. GLP-1 receptor agonists were permitted up to the dose approved for treatment of diabetes mellitus. Medications that could theoretically cause weight loss were allowed as long as the patient (1) had used them at a stable dose for at least 3 months prior to randomisation, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable during the study.	Patients were allowed to continue with other chronic concomitant medications. Medications commonly used in obese patients could also be continued if the patient was taking a stable dose. Medications that could impact on efficacy assessment, such as anorectic agents or drugs with anorexia as a non-rare side effect were prohibited; low-threshold drugs were not permitted.
Primary outcomes	The primary efficacy endpoint was the proportion of patients aged ≥12 years who achieved a ≥10% reduction in body weight from baseline after ~52 weeks of treatment.	The primary endpoint was the safety and tolerability of setmelanotide.
Other outcomes used in the economic model	Other efficacy endpoints comprised: change in body weight; change in daily hunger score; the proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25%; the proportion of patients who achieved a ≥10% reduction in body weight; composite response rate (a ≥10% reduction in body weight or ≥25% improvement in daily hunger score); the proportion of patients meeting categorical weight loss thresholds of 5%, 15%, 20%, 25%, 30%, 35%, and 40%; the proportion of patients achieving a ≥10% reduction in body weight or ≥15% reduction in BMI; change of BMI Z-score in paediatric patients; change in waist circumference; change in total body mass; global hunger response; change in PWS-FPD and PWS-SEQ; change in insulin sensitivity/resistance; change in fasting lipids; SF-36V2 and SF-10 domain and composite summary score; PedsQL or IWQOL-Lite, age-dependent, and EQ-5D score. Setmelanotide safety and tolerability was also assessed.	No secondary endpoints were specified for this study. Exploratory endpoints included: the proportion of patients with ≥10% weight loss; hunger score; body composition; waist circumference; lipid levels; quality of life; biomarkers predictive of a setmelanotide response; C-SSRS and PHQ-9 scores.
Pre-planned subgroups	Disease type (BBS and AS) and age of paediatric subjects (<12 years and <18 years)	Not applicable

B.2.3.3 Patient characteristics

Study RM-493-023

A summary of demographic and baseline information is presented for all patients with BBS (pivotal and supplemental) in Table 12. The mean age of the BBS population at the start of the trial was 20 years of age, across a range of 6 to 46 years. Slightly more females than males were enrolled. Most patients were White. Mean BMI at baseline was ≥40 kg/m^2, which aligns with the US Centers for Disease Control and Prevention criteria for severe (Class III) obesity. Of note, baseline most/worst hunger scores differed significantly between setmelanotide and placebo groups. Baseline hunger in the setmelanotide arm was 4.7 compared with 6.8 for placebo.

Table 12 BBS patient characteristics on inclusion (Study RM-493-023, pivotal and supplemental patients)

	Setmelanotide (N=22)	Placebo (N=22)	Total (N=44)
Mean (SD) [range] age, years[1]	18.5 (9.7) [6, 42]	21.5 (12.6) [6, 46]	20.0 (11.2) [6, 46]
Age group, n (%)			
≥18 years	10 (45.5)	12 (54.5)	22 (50.0)
<18 years old	12 (54.5)	10 (45.5)	22 (50.0)
Female n (%)	9 (40.9)	15 (68.2)	24 (54.5)
Race, n (%)			
White	15 (68.2)	19 (86.4)	34 (77.3)
Black or African American	1 (4.5)	1 (4.5)	2 (4.5)
Asian	0 (0.0)	1 (4.5)	1 (2.3)
Other	6 (27.3)	1 (4.5)	7 (15.9)
Ethnicity, n (%)			
Non-Hispanic and non-Latin	1 (4.5)	0 (0.0)	1 (2.3)
Hispanic or Latin	18 (81.8)	19 (86.4)	37 (84.1)
Not reported	1 (4.5)	2 (9.1)	3 (6.8)
Unknown	2 (9.1)	1 (4.5)	3 (6.8)
Mean (SD) [range] weight, kg[1]	110.45 (35.8) [46.4, 173.8]	106.5 (31.8) [47.0, 166.0]	108.5 (33.5) [46.4, 173.8]
Mean (SD) [range] BMI, kg/m^2 [1]	41.4 (10.0) [24.4, 61.3]	41.6 (10.1) [24.6, 66.1]	41.5 (9.9) [24.4, 66.1]
Patients aged ≥12 years without cognitive impairment completing the daily hunger questionnaire, n (%)	7 (31.8)	12 (54.5)	19 (43.2)
Most/worst hunger, mean (SD) [n][2]	4.7 (1.6) [7][1]	6.8 (2.0) [12][1]	6.8 (1.8) [18][3]

[1] Placebo-controlled period baseline.
[2] Patients aged ≥12 years without cognitive impairment; self reported. Assessed daily using a numeric rating score from 0 to 10, with 0 = not hungry at all and 10 = hungriest possible.
[3] At active treatment baseline.

The baseline distribution of patients by BMI category (adult patients) and BMI *Z*-score category (paediatric patients) is presented in Table 13.

Table 13 Baseline BMI and BMI Z-score categories for BBS patients (Study RM-493-023, pivotal patient SAS)

Baseline BMI (kg/m^2) / BMI Z-score category	BMI in BBS patients aged ≥18 years (N=16)	BMI Z-score in BBS patients aged <18 years (N=16)
BMI 20 to ≤25 / BMI Z 1 to ≤ 2	[redacted]	[redacted]
BMI 25 to ≤30 / BMI Z 2 to ≤2.5	[redacted]	[redacted]
BMI 30 to ≤35 / BMI Z 2.5 to ≤3	[redacted]	[redacted]
BMI 35 to ≤40 / BMI Z 3 to ≤3.5	[redacted]	[redacted]
BMI 40 to ≤45 / BMI Z 3.5 to ≤4	[redacted]	[redacted]
BMI 45 to ≤50 / BMI Z 4+	[redacted]	[redacted]
BMI 50+	[redacted]	[redacted]

Study RM-493-022

The characteristics of BBS patients included in Study RM-493-022 who were classified as setmelanotide responders are summarised in Table 14. Data for all 42 BBS patients included in Study RM-493-022 are presented in Appendix M. Seven responders had previously been treated in Study RM-493-014 and 23 responders had been treated in Study RM-493-023.

Mean age at inclusion in the index study was 19 years (range 6 to 61 years). Slightly more patients were female than male. The majority were White and mean BMI at index study baseline was approximately 40 kg/m^2.

Table 14 BBS responder characteristics on inclusion into Study RM-493-022

		Setmelanotide responders (N=30)
Mean (SD) [range] age at index study baseline, years		[redacted]
Age categories at index trial baseline, n (%)	<18 years	[redacted]
	≥18 years	[redacted]
Sex, n (%)	Male	[redacted]
	Female	[redacted]
Race, n (%)	White	[redacted]
	Black / African American	[redacted]
	Asian	[redacted]
	Other	[redacted]
Mean (SD) [range] weight at index study baseline, kg		[redacted]
Mean (SD) [range] BMI at index study baseline, kg/m^2		[redacted]
Mean (SD) [range] BMI Z-score at index study baseline in patients aged <18 years		[redacted]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Study RM-493-023

Sample size

The sample size for Study RM-493-023 was mainly driven by the primary hypothesis, although the rarity of the patient population was also taken into consideration. Data from CRIBBS were used to provide input for the sample size/power calculations.

The primary statistical hypothesis was that the proportion of patients (aged ≥12 years) treated for ~52 weeks who achieve ≥10% reduction from baseline in body weight would be greater than a historical control rate of 10% in the Full Analysis Set (FAS). The null hypothesis (H0) was that the proportion of patients treated for ~52 weeks who achieved ≥10% reduction in body weight from baseline would be less than or equal to a historical control rate of 10%. Please note that there are 2 different uses of '10%' above, as explained here for clarity:

- The use of 10% in the endpoint definition is the response criterion for an individual patient. If a patient achieves a ≥10% reduction from baseline in body weight, the

patient is categorised as a responder. Otherwise, the patient is categorised as a non-responder.

- The use of 10% as the historical control rate is the historical reference/control rate to be statistically compared with the observed response rate in patients treated with setmelanotide (i.e., the proportion of patients with BBS who lose at least 10% of body weight with no intervention). The observed setmelanotide response rate was calculated as the number of responders (using the 10% endpoint definition) divided by the total number of patients.

For the primary hypothesis a sample size of 7 patients would provide ~91% power at a 1-sided alpha level of 0.025 to show a statistically significant difference, assuming a 66% anticipated response rate in patients treated with setmelanotide (based on a preliminary review of data from the then ongoing Phase 2 Study RM-493-014) compared with a 10% historical control rate (based on data from the CRIBBS registry). A 1-sided alpha level of 0.025 was chosen as the scientific success criterion associated with the primary analysis.

Although these data suggest that powering the study for the primary endpoint would require a small number of patients (N <10), the size of the trial also reflected the rarity of BBS and AS and a desire to better understand the effect of setmelanotide in these patients. Hence, it was planned to enrol approximately 30 patients (including 6 patients with AS) in the study. This number was deemed suitable for a single pivotal trial to support the BBS and AS indications and to provide robust data for both between-group analysis of the placebo-controlled, double-blinded period (Period 1) and the one-sample comparison versus the historical-control response rate after the last patient had completed the planned 38-week, open-label treatment period.

No formal interim analysis was planned or performed and no stopping guidelines were specified. No adjustments were made for covariates.

Analysis populations

Analysis populations specified for Study RM-493-023 are summarised in Table 15.

Table 15 Study RM-493-023 analysis sets

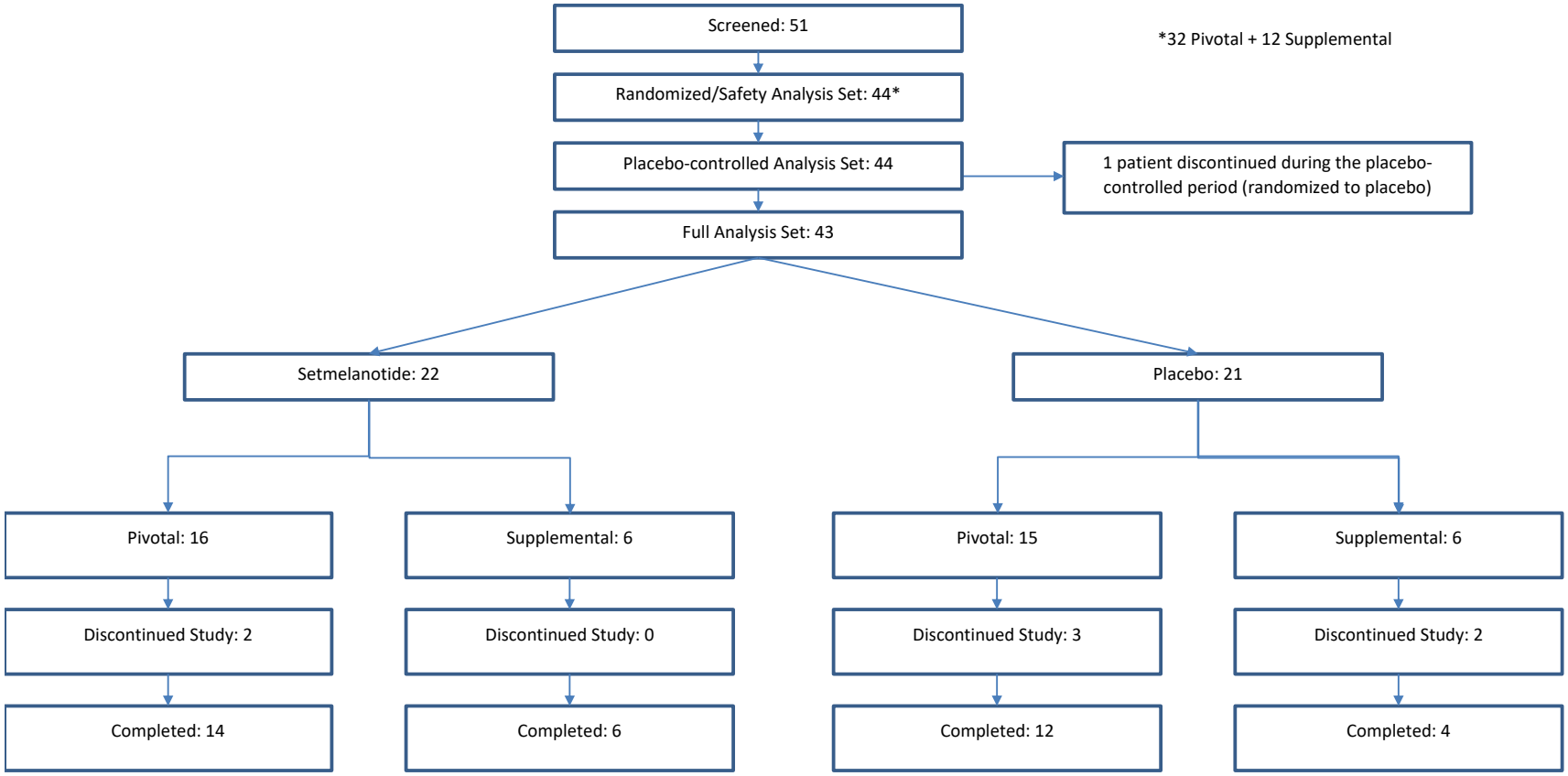
Analysis set	Definition	Use	Baseline for efficacy analyses
Screening set	All patients who signed informed consent		
Safety analysis set (SAS)	All patients who received at least 1 dose of study drug (placebo or setmelanotide).	Safety endpoints. Patient data were analysed according to the treatment received.	
Full analysis set (FAS)	All patients (irrespective of age) who received at least 1 setmelanotide dose and provided baseline data	Efficacy endpoints	Active treatment baseline (ATB) - the last available measurement prior to the first dose of setmelanotide
Placebo-controlled analysis set (PCAS)	All randomised patients who received at least 1 dose of placebo or setmelanotide and provided baseline data	Data from the 14-week placebo-controlled, double-blind period (Period 1). PCAS analyses were performed based on patients as randomised.	Placebo-controlled period baseline (PCPB) - the last available measurement prior to the first dose of setmelanotide or placebo

Patient flow

Two cohorts of patients were enrolled in Study RM-493-023. The initial cohort, comprised the first 32 patients enrolled with BBS and is referred to as the pivotal cohort. For the pivotal cohort, data are available for all patients (including those randomised to placebo) up to approximately 52 weeks of treatment with setmelanotide. The pivotal cohort therefore provides data for 52-week efficacy analyses.

A supplemental cohort of 12 patients with BBS was also enrolled, however these patients were permitted to exit Study RM-493-023 and enrol in long-term extension Study RM-493-022 from Week 24. Since all supplemental patients completed the 14-week double-blind period, results for all patients (pivotal and supplemental) are included in the 14-week analyses. Figure 5 gives an overview of patient flow through the study.

Figure 5 BBS patient flow in Study RM-493-023



Of the 44 BBS patients entering Study RM-493-023, most (81.8%) completed the study as planned (Table 16). The frequency of patients who discontinued the study early was higher in the placebo group (27.3% vs 9.1% in the setmelanotide group) with AEs cited as the most frequent reason for early discontinuation in the placebo group (13.6% vs 0.0%).

Table 16 BBS patient disposition in Study RM-493-023

Parameter	Overall, n (%)		Pivotal, n (%)		Supplemental, n (%)	
	Setmelanotide N=22	Placebo N=22	Setmelanotide N=16	Placebo N=16	Setmelanotide N=6	Placebo N=6
Completed	[redacted]	[redacted]	14 (87.5)	12 (75.0)	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	2 (12.5)	4 (25.0)	[redacted]	[redacted]
Primary reason for early discontinuation						
Adverse event	[redacted]	[redacted]	0 (0.0)	3 (18.8)	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	1 (6.3)	1 (6.3)	[redacted]	[redacted]
Withdrawal	[redacted]	[redacted]	1 (6.3)	0 (0.0)	[redacted]	[redacted]
Transfer to extension trial	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	[redacted]

[1] Supplemental patients were considered completed if they enrolled in the extension trial; however, 2 patients enrolled in the extension trial and were counted as discontinued.

In total, [redacted] BBS patients discontinued Study RM-493-023:

- In the setmelanotide group: [redacted] was lost to follow up after having previously been discontinued from treatment by his parents after AEs of headache, leg pain and belligerent behaviour; [redacted] withdrew from the study having previously discontinued treatment due to lack of efficacy.
- In the placebo group: [redacted] due to AEs (anaphylaxis; nausea, hot flashes, headache, vomiting, and abdominal pain; nausea and vomiting); [redacted] supplemental patients enrolled in the extension trial and were specified as discontinued; and [redacted] lost to follow-up.

Endpoint analysis

Study endpoints and the analysis methods used are described in Table 17.

Table 17 Statistical analyses conducted for Study RM-493-023

Endpoint	Timeframe	Population	Null hypothesis	Method
Proportion of patients achieving ≥5% or ≥10% reduction in body weight	Baseline to 52 weeks	BBS patients aged ≥18 years	The proportion was not greater than a historical control rate of 10%	Binomial proportions were calculated for each of 100 imputed datasets. Outcomes from imputed datasets were combined using Rubin's rule to provide an overall estimate against the null hypothesis with CIs and a corresponding p-value.
Mean and mean percent change in body weight and BMI	Baseline to 52 weeks	BBS patients aged ≥18 years		A one-sample t-test for each of 100 imputed datasets, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented.
Mean and mean percent change in BMI and BMI Z-score	Baseline to 52 weeks	BBS patients aged <18 years		
Proportion of patients in the BMI 95th weight percentile	Baseline to 52 weeks	BBS patients aged <18 years		
Mean and percent change in the weekly average of the daily hunger score	Baseline to 52 weeks	BBS patients aged ≥12 years (daily hunger score was not collected in patients with cognitive impairment)		A one-sample t-test for each of 100 imputed datasets, assuming a mean change of 0 from baseline. The outcomes from imputed datasets were combined using Rubin's rule to provide CIs and a p-value (evaluated at a one-sided, 0.025 significance level). If statistical analysis was not performed, descriptive statistics were presented.

Endpoint	Timeframe	Population	Null hypothesis	Method
Daily hunger score	Baseline to 52 weeks	BBS patients aged ≥12 years (daily hunger score was not collected in patients with cognitive impairment)		Each of the 3 hunger assessments (most/worst, morning, and average over 24 hours) were averaged separately by week
Proportion of patients with a ≥25% improvement in the weekly average of daily hunger score	Baseline to 52 weeks	FAS		The p-value after 52 weeks of treatment was analysed using binomial proportions calculated for each of 100 imputed datasets. Outcomes from the 100 imputed datasets were combined using Rubin's rule to provide an overall estimate.
Weekly average of daily hunger scores by visit; PW-FPD in patients with cognitive impairment; quality of life; waist circumference; and lipid parameters	Baseline to 52 weeks	FAS		Descriptive statistics

Between-group comparison was used to investigate whether setmelanotide treatment of patients with BBS resulted in:

- A greater decrease in percent change in body weight, BMI, BMI Z-score, and BMI 95th percentile score from the placebo-controlled period baseline after 14 weeks of therapy vs placebo treated patients.
- Greater improvement in the weekly average of daily hunger scores (most/worst, average over 24 hours, morning hunger) from baseline after 14 weeks of therapy vs placebo treated patients.

Analyses were based on a two-sample t-test for each of the 100 imputed datasets, with an assumed mean percent change from baseline in the select parameter score of zero. Outcomes from the 100 imputed datasets were combined using Rubin's rule to provide CIs and a corresponding p-value, which was evaluated at a one-sided, 0.025 significance level.

Missing data

The nature of the study meant that a small proportion of patients randomised to placebo could have had less than ~52 weeks of setmelanotide treatment at the time of the primary analysis (defined as when the last patient enrolled had completed the 38-week open-label treatment period; these patients did not complete 52 weeks of setmelanotide treatment until Week 66 of the study). Hence, the primary analysis included a multiple imputation model (SAS PROC MI) to impute weight measurements for patients with less than ~52 weeks of setmelanotide treatment to a timepoint that approximated to 52 weeks. The final multiple imputed datasets were analysed using Rubin’s rule (with SAS PROC MIANALYZE).

Patients could also have missing data for other reasons (loss to follow up, early discontinuation, missed visit, AEs, etc.). In these cases, the same principle and multiple imputation approach was used to impute the missing value. However, for primary and key secondary analyses, imputed values were replaced with the patient’s baseline value (constituting a treatment failure approach as the effective change from baseline would equate to zero).

Missing values in the 14-week placebo-controlled, double-blinded treatment period were imputed with a similar multiple imputation approach as defined for the primary endpoint.

Study RM-493-022

No formal hypothesis was specified for open-label extension study RM-493-022. As the study was to enrol eligible patients who completed a previous setmelanotide study, sample size estimation was not relevant. As this patient group is extremely rare, efforts were made to include all data in all endpoint analyses. No missing data were imputed and analyses were conducted using all available data. With respect to exploratory endpoints, no adjustments for multiplicity were included.

Participant flow

A total of 30 patients with BBS who responded to setmelanotide in a previous trial were included in Study RM-493-022, of whom, 3 patients (10.0%) had discontinued treatment by the study data cut-off (June 2022, Table 18).

Table 18 Patient disposition in Study RM-493-022

	Setmelanotide responders N = 30, n (%)
Ongoing in Study RM-493-022	[redacted]
Discontinued	[redacted]
Primary reason for treatment/study discontinuation	
Adverse event	[redacted]
Withdrawal by patient	[redacted]
Entered another setmelanotide trial	[redacted]

Study RM-493-022 is ongoing and therefore at the time of reporting not all patients had completed the full 3 years of setmelanotide treatment. The numbers of patients providing data for analysis at each of the time points therefore varies, as summarised in Table 19.

Table 19 Numbers of patients included in Study RM-493-022 analyses at each time point

	All responders	All adult responders	All paediatric responders
Included from index trial	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]

Appendix D presents details of the numbers of participants eligible to enter the studies.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of pivotal Study RM-493-023 is presented in Table 20, with consideration of the long-term extension Study RM0493-022 presented in Table 21.

Table 20 Quality assessment of Study RM-493-023

Study question	Response	How is the question addressed in the study?
Was the randomisation method adequate?	Yes	Eligible patients were assigned a unique randomisation number via an interactive website response system based on a randomisation code generated prior to the start of the study. Patients were randomised in a 1:1 ratio, stratified by age group (≥12 years or <12 years) and disease (BBS or AS), to receive either setmelanotide or placebo during the first 14 weeks of the study.
Was allocation adequately concealed?	Yes	Placebo comprised setmelanotide vehicle for subcutaneous injection. Placebo and setmelanotide were indistinguishable to ensure blinded treatment.
Were groups similar at the outset of the study in terms of prognostic factors?	Yes	The setmelanotide and placebo groups were comparable in terms of baseline weight and BMI.
Were care providers, participants and outcome assessors blind to treatment allocation?	Yes	Blinding was established so that all patients and study-related staff remained blinded for the duration of the 14-week, double-blind treatment period; blinding was also maintained throughout the 38-week open-label treatment period. To maintain the blind, dose escalation to a fixed dose of 3 mg was to be repeated for all patients at the start of the 38-week, open-label treatment period. No data from the 14-week placebo-controlled, double-blind period were to be unblinded (except for safety reasons) until the 38-week, open-label treatment period had completed.
Were there any unexpected imbalances in drop-outs between groups?	Yes	A slightly higher proportion of patients in the placebo group discontinued the study (27% vs 9% in the setmelanotide group). However, this included 2 supplemental patients who were recorded as discontinued despite having entered the extension study.
Is there evidence to suggest that the authors measured more outcomes than they reported?	No	The main outcome measures are presented in the body of the clinical study report, with other assessments detailed in the associated tables and listings.

Study question	Response	How is the question addressed in the study?
Did analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary endpoint was assessed using the FAS. The FAS comprised patients who received at least 1 setmelanotide dose and had baseline data. This population included patients who did not complete the study for any reason. The nature of the study meant that a small proportion of placebo patients could have had less than ~52 weeks of setmelanotide treatment at the time of the primary analysis. Hence, the primary analysis included a multiple imputation model to impute weight measurements for these patients to a timepoint that approximated 52 weeks. For primary and key secondary analyses patients with missing data for other reasons had imputed values replaced with the patient baseline value, constituting a treatment-failure approach. Sensitivity analyses used the following methods: • For primary and key secondary endpoints, multiple imputation imputed 52-week values were used for all patients with missing 52-week data. • The proportion of patients (aged ≥12 years) achieving ≥10% reduction in body weight was also assessed using a placebo-completer's analysis that excluded data for placebo patients who had not completed ~52 weeks of setmelanotide treatment by Week 52. • Daily hunger scores were included for patients with at least 3 of 7 days of data with no imputation of missing data. • Comparison of setmelanotide- and placebo-treated patients after ~14 weeks was assessed using a sensitivity failure analysis, in which patients with missing 14-week data were considered treatment failures.

Table 21 Quality assessment of Study RM-493-022

Study question	Response	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	All patients in this extension trial had received setmelanotide in a prior trial.
Was exposure accurately measured to minimise bias?	Yes	All patients in this trial received setmelanotide which was self-administered at the dose agreed by the study clinician
Was the outcome accurately measured to minimise bias?	Yes	All measurements were done in triplicate at each timepoint and whenever possible the same scale was used throughout the study which was calibrated on a regular basis. Weight was to be measured when patients were fasting and at approximately the same time at each visit
Have the authors identified all important confounding factors?	N/A	The study has not been published
Have the authors taken account of confounding factors in the design and/or analysis?	Yes	Weight-related parameters were analysed for adult (aged ≥18 years old) paediatric (aged <18 years) subgroups separately to minimise the confounding and dilution of treatment effect that would occur by mixing the paediatric population, which is still growing, with the adult population
Was patient follow-up complete?	No	The study is still ongoing
How precise are the results?		At month 36 (n=12), the 90% CI for change in BMI from index study baseline was [redacted], [redacted]

B.2.6 Clinical effectiveness results of relevant studies

B.2.6.1 Study RM-493-023

Study RM-493-023 was conducted in both BBS and AS patients but marketing authorisation was not sought for AS patients, and this submission relates only to the use of setmelanotide in BBS patients. However, the primary endpoint is presented for the full trial population (BBS and AS patients) in addition to BBS patients only; all other data are presented for the BBS population only.

Results throughout this section are presented separately for patients aged ≥18 years and those aged <18 years. In growing children, body weight is heavily influenced by physical development and maturation. Body weight is, therefore, primarily used for patients aged ≥18 years, whilst weight-related parameters that account for differences in height (such as BMI) and those that account for differences in age and sex (such as BMI Z-score and the percentage of the BMI 95th percentile score) are used for patients aged <18 years.

In order to inform the economic model, a post-hoc analysis was carried out to determine the proportion of patients aged ≥18 years who moved from one BMI category to another and the proportion of patients aged <18 years who moved from one BMI Z-score category to another. Only data from setmelanotide 'responders' (i.e. adult patients who achieved ≥10% weight loss or paediatric patients who achieved ≥0.2 reduction in BMI Z-score after 52 weeks of setmelanotide treatment) were used to inform on these transitions, as patients who do not meet such thresholds would not continue setmelanotide treatment in clinical practice. Of the 15 pivotal adult patients in Study RM-493-023, 7 were considered responders; of the 16 paediatric patients, 12 were considered responders.

B.2.6.1.1 Primary end point

Proportion of pivotal patients aged ≥12 years who achieved a ≥10% reduction in body weight after 52 weeks of setmelanotide treatment

The primary endpoint for Study RM-493-023 comprised the proportion of pivotal patients (BBS and AS) aged ≥12 years in the FAS population who achieved a clinically-meaningful reduction in body weight (≥10%) from active-treatment baseline after ~52 weeks of setmelanotide treatment (Table 22). The estimated proportion (32.3%) of pivotal patients ≥12 years of age with BBS or AS who achieved a ≥10% reduction in body weight from the active-treatment baseline was statistically significant (p=0.0006) compared with a historical control rate of 10%; the study, therefore, met its primary efficacy endpoint.

Table 22 Proportion of BBS or AS patients aged ≥12 years who achieved a ≥10% reduction in body weight (Study RM-493-023, pivotal BBS and AS patient FAS)

	BBS and AS patients aged ≥12 years
N	31
Proportion, % (95% CI) p-value	32.3 (16.7, 51.4) 0.0006

Analysis of the primary endpoint for BBS patients is presented in Table 23.

Approximately [redacted]% of BBS patients aged ≥12 years achieved a ≥10% reduction in body weight from the active-treatment baseline after ~52 weeks of setmelanotide along with 47% of patients aged ≥18 years.

Table 23 Proportion of BBS patients aged ≥12 years or ≥18 years with a 10% reduction in body weight (Study RM-493-023, pivotal patient FAS)

	BBS patients aged ≥12 years	BBS patients aged ≥18 years
N	28	15
Proportion, % (95% CI) p-value	[redacted]	46.7 (21.3, 73.4) 0.0003

B.2.6.1.2 14-week, double-blind treatment period, placebo-controlled study results (BBS patients)

The 14-week randomised-controlled data demonstrated that setmelanotide is effective at reducing hunger and inducing weight loss compared with placebo:

- Patients of all ages treated with setmelanotide saw a mean decrease in hunger score of [redacted]% compared with [redacted]% for those receiving placebo.
- Patients aged ≥18 years treated with setmelanotide lost a mean of 5.52 kg (3.93% of body weight) compared with 0.48 kg (0.34% body weight) for those receiving placebo.
- Patients of all ages treated with setmelanotide had a mean reduction in BMI of [redacted] kg/m^2 compared with [redacted] kg/m^2 for those who received placebo.

Mean change in daily hunger after 14 weeks of setmelanotide treatment compared with placebo

In patients aged ≥12 years without cognitive impairment, setmelanotide treatment over 14 weeks resulted in numerically greater reductions from the placebo-controlled period baseline in hunger score over 24 hours (Table 24). This finding is supportive of the proposed setmelanotide mechanism of action; by restoring activity to the MC4R pathway responsible for controlling feelings of hunger and satiety, setmelanotide reduces the hyperphagia experienced by BBS patients thereby acting supporting future weight loss and BMI/BMI Z-score reduction.

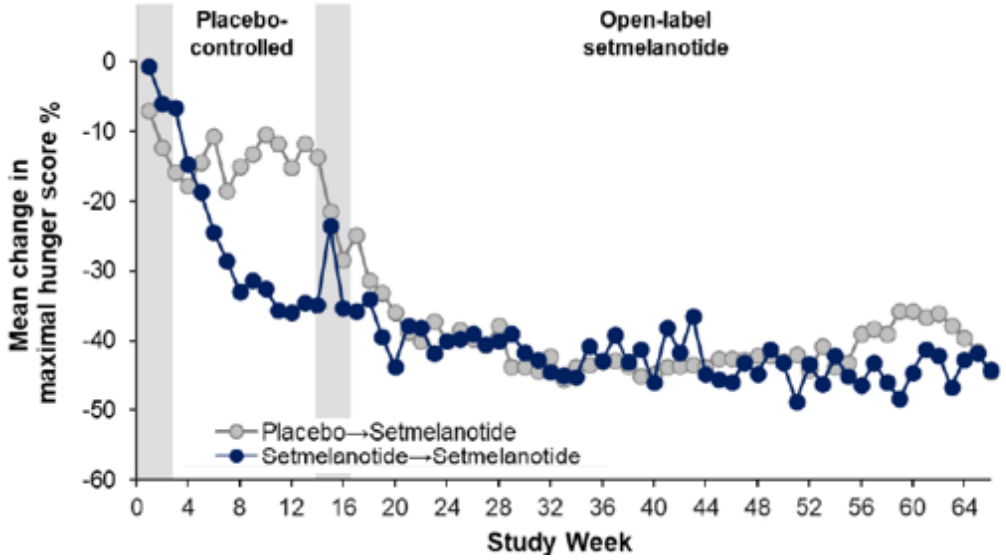
Table 24 Change in the weekly average of daily hunger score from baseline after 14 weeks of setmelanotide treatment in BBS patients aged ≥12 years without cognitive impairment (Study RM-493-023, all patient PCAS)

Group/parameter	Statistic	Setmelanotide	Placebo
Most/worst hunger over 24 hours		(N = 7)	(N = 12)
Weekly average at PCPB	N		
	Mean (SD)		
	Median (range)		
Weekly average change	N		
	Mean (SD)		
	Median (range)		
	95% CI		
	Difference (95% CI)		
	p-value		
Weekly average percent change	N	6	12
	Mean (SD)		
	Median (range)		
	95% CI		
	Difference (95% CI)		
	p-value		
Average hunger over 24 hours		(N = 18)	(N = 18)
Weekly average at PCPB	N		
	Mean (SD)		
	Median (range)		

Group/parameter	Statistic	Setmelanotide	Placebo
Weekly average change	N	6	12
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	
Weekly average percent change	N	6	12
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	
Morning hunger		(N=18)	(N=18)
Weekly average at PCPB	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Weekly average change	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	
Weekly average percent change	N	6	12
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	

Mean change in maximal hunger score over the course of treatment is presented in Figure 6.

Figure 6 Mean change in maximal hunger score in patients aged ≥12 years without cognitive impairment (Study RM-493-023, pivotal patients with BBS)



Grey bars indicate titration and re-titration periods.

Mean change in body weight after 14 weeks of setmelanotide treatment compared with placebo

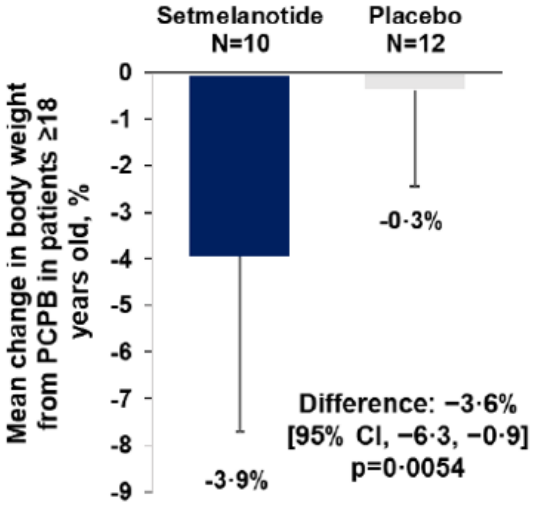
In all BBS patients (pivotal and supplemental) aged ≥18 years, treatment with setmelanotide over 14 weeks resulted in significantly greater reduction in body weight from the placebo-controlled period baseline compared with placebo-treated patients (Table 25). Patients receiving setmelanotide had a mean reduction in body weight of [redacted] kg, whilst mean weight for the placebo group remained virtually unchanged from baseline ([redacted] kg) over the 14-week treatment period.

Table 25 Change in body weight from baseline after 14 weeks of setmelanotide treatment in BBS patients aged ≥18 years (Study RM-493-023, all patient PCAS)

Parameter	Statistic	Setmelanotide (N = 10)	Placebo (N = 12)
Body weight at PCPB (kg)	N	10	12
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Change after 14 weeks (kg)	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	
Percent change after 14 weeks (kg)	N	10	12
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	p-value	[redacted]	

Change in body weight after 14 weeks of setmelanotide treatment is presented in Figure 7.

Figure 7 Change in body weight after 14 weeks of setmelanotide treatment in BBS patients aged ≥18 years (Study RM-493-023, all patient PCAS)



Change in BMI after 14 weeks of setmelanotide treatment compared with placebo

Setmelanotide treatment over 14 weeks resulted in a statistically significant reduction in BMI compared with patients who received placebo (Table 26), for the 44 patients in the pivotal and supplemental cohorts. Patients who received setmelanotide lost a mean of [redacted] kg/m^2 over 14 weeks compared with [redacted] kg/m^2 for those who received placebo.

Table 26 Change in BMI after 14 weeks of setmelanotide treatment for patients with BBS (Study RM-493-023, all patient PCAS)

Parameter	Statistic	Setmelanotide (N = 22)	Placebo (N = 22)
BMI at PCPB (kg/m^2)	N	22	22
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Change after 14 weeks (kg/m^2)	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	One-sided p-value	[redacted]	
Percent change after 14 weeks	N	22	22
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Difference (95% CI)	[redacted]	
	One-sided p-value	[redacted]	

Figure 8 presents the percent change in BMI from baseline for all patients over 14-weeks; those who received setmelanotide are shown in blue and those who received placebo in red. [redacted] of the setmelanotide-treated patients had a percent reduction in BMI from the placebo-controlled period baseline to Week 14; in contrast, [redacted] of placebo-treated patients showed reductions, with [redacted] gaining weight.

Figure 8 Waterfall plot of percent change in BMI from baseline to Week 14 (Study RM-493-023, all BBS patient PCAS)

B.2.6.1.3 Open-label extension period – 52-week data (BBS patients)

Findings from the open-label extension period of study RM-493-023 demonstrated that the reductions in hunger seen during the 14-week placebo-controlled period were sustained and weight loss continued with up to 52 weeks of setmelanotide treatment:

- At 52 weeks, mean change from baseline in maximal hunger was -30.9% (p=0.0001) across all age groups.
- Patients aged ≥18 years lost an average of 9.4kg (7.6%) and had a BMI reduction of 4.2 kg/m^2 (9.1%).
- Patients aged <18 years had an average BMI reduction of 3.4 kg/m^2 (9.5%) or a reduction of 0.8 in BMI Z-score.

Change in the weekly average of daily hunger score after 52 weeks of setmelanotide treatment (BBS patients)

Setmelanotide treatment over 52 weeks resulted in significantly greater reductions from active-treatment baseline (compared with a reference value of 0) in the mean weekly average of daily hunger score in pivotal patients aged ≥12 years without cognitive impairment (Table 27). Patients had a mean weekly average reduction in most/worst hunger of 2.12 points on the 10-point scale.

Table 27 Change in the weekly average of daily hunger score from baseline after 52 weeks of setmelanotide treatment in BBS patients aged ≥12 years without cognitive impairment (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic [1]	Average hunger over 24 hours	Most/worst hunger over 24 hours	Morning hunger
Weekly average baseline	N	14	14	14
	Mean (SD)	[redacted]	6.99 (1.893)	[redacted]
	Median (range)	[redacted]	7.29 (4.0, 10.0)	[redacted]
Weekly average change	N	14	14	14
	Mean (SD)	[redacted]	-2.12 (2.051)	[redacted]
	Median (range)	[redacted]	-1.69 (-6.7, 0.0)	[redacted]
	95% CI	[redacted]	-3.31, -0.94	[redacted]
	p-value	[redacted]	0.0010	[redacted]
Weekly average percent change	N	14	14	14
	Mean (SD)	[redacted]	-30.45 (26.485)	[redacted]
	Median (range)	[redacted]	-25.00 (-77.0, 0.0)	[redacted]
	95% CI	[redacted]	-45.74, -15.16	[redacted]
	p-value	[redacted]	0.0004	[redacted]

[1] 95% CI and p-value based on Rubin's rule.

An estimated 57.1% of pivotal BBS patients aged ≥12 years without cognitive impairment achieved a ≥25% improvement in the weekly average of daily hunger score, which was statistically significant compared with a reference value of 0 ($p<0.0001$, Table 28). Based on psychometric analysis, the most appropriate, meaningful, within-patient threshold for most/worst hunger score is a reduction of 1 to 2 points across the populations in whom setmelanotide has been tested in pivotal trials. Note that a most/worst hunger score of zero is not desirable as this would indicate that patients

were never hungry. The aim of treatment is to reduce the level of hunger between meals so that patients are not driven to eat after having just finished a meal. Maintaining an appropriate level of most/worst hunger is necessary to ensure that patients want to eat in an appropriate manner/at an appropriate time.

Table 28 Proportion of BBS patients aged ≥12 years without cognitive impairment who achieved ≥25% improvement in the weekly average of daily hunger score after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal patient FAS)

	N=14
Estimate % (95% CI)	57.1 (28.9, 82.3)
p-value	<0.0001

Change in body weight after 52 weeks of setmelanotide treatment (BBS patients)

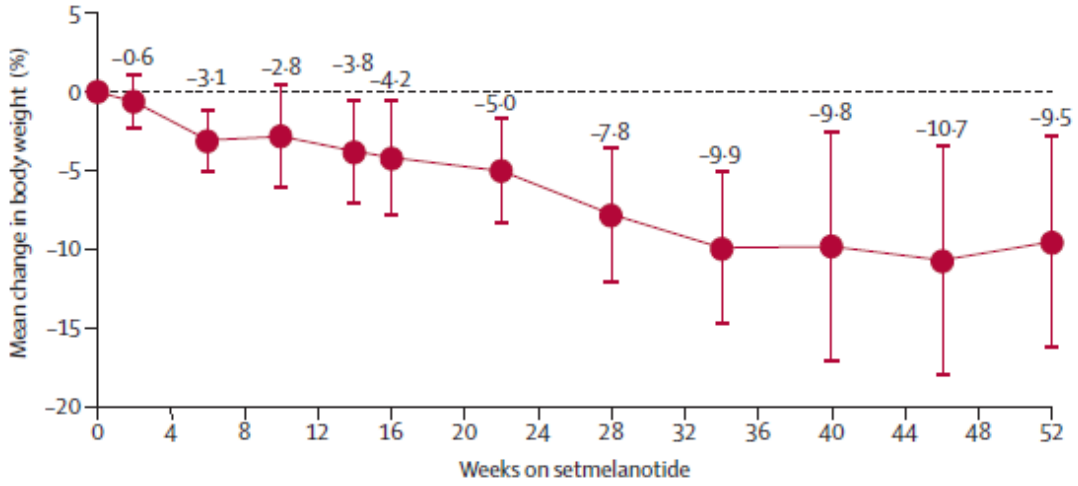
In pivotal patients aged ≥18 years, 52 weeks of setmelanotide treatment resulted in a significant reduction from active-treatment baseline in body weight compared with the reference value of 0% reduction (Table 29). The reduction in body weight over time is presented in Figure 9. Mean weight loss at Week 52 was -9.42 kg and mean percent change was -7.57%; a change of ≥5% is considered clinically meaningful (European Medicines Agency, 2017; Food and Drug Administration, 2007; Garvey 2016; Ryan 2017).

Table 29 Change in body weight from baseline after 52 weeks of setmelanotide treatment in BBS patients aged ≥18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic[1]	Result
Body weight at ATB (kg)	N	15
	Mean (SD)	128.43 (16.591)
	Median (range)	129.83 (105.2, 167.3)
Change after 52 weeks (kg)	N	15
	Mean (SD)	-9.42 (9.393)
	Median (range)	-8.13 (-27.0, 7.5)
	95% CI	-14.63, -4.22
	p-value	0.0008
Percent change after 52 weeks	N	15
	Mean (SD)	-7.57 (7.139)
	Median (range)	-6.16 (-18.6, 4.5)
	95% CI	-11.52, -3.62
	p-value	0.0005

[1] 95% CI and p-value based on Rubin's rule.

Figure 9 Mean change in body weight from active-treatment baseline in BBS patients aged ≥18 years (Study RM-493-023, pivotal patient FAS)



Change in BMI Z-score after 52 weeks of setmelanotide treatment (BBS patients)

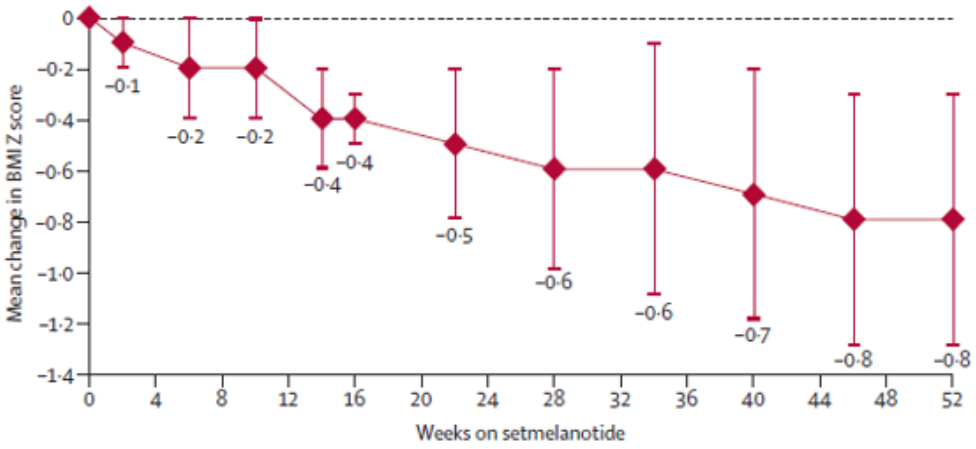
In pivotal BBS patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a significantly greater reduction in mean change in BMI Z-score from active-treatment baseline as compared with a reference value of 0% reduction (Table 30). Mean change

over time is presented in Figure 10. The mean change in BMI Z-score at Week 52 was -0.75 points. Literature data suggest that a reduction in BMI Z-score of at least -0.15 to -0.20 is clinically meaningful in paediatric patients (Ells 2018; U.S. Preventative Services Task Force 2017; Wiegand 2014). The approved weight management drug, Saxenda®, was licensed based on a reduction of -0.23 in mean BMI Z-score after 56 weeks of treatment (Saxenda USPI, 2020).

Table 30 Change in BMI Z-score from baseline after 52 weeks of setmelanotide treatment in BBS patients aged <18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result
BMI Z-score at ATB	N	16
	Mean (SD)	3.74 (1.339)
	Median (range)	3.54 (1.8, 7.1)
Change after 52 weeks	N	14
	Mean (SD)	-0.75 (0.458)
	Median (range)	-0.77 (-1.9, -0.2)
	95% CI	-1.02, -0.49
	p-value	<0.0001

Figure 10 Mean change in BMI Z-score from active treatment baseline in BBS patients <18 years (Study RM-493-023, pivotal patient FAS)



Overall, 85.7% of BBS patients aged <18 years achieved at least a 0.2-point reduction from baseline in BMI Z-score with setmelanotide treatment and 71.4% achieved at least a 0.3-point reduction (Table 31).

Table 31 Proportion of BBS patients aged <18 years achieving a BMI Z-score reduction from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result
≥0.2 change from ATB (n=14)	n (%)	12 (85.7)
	(95% CI)	(57.2, 98.2)
≥0.3 change from ATB (n=14)	n (%)	10 (71.4)
	(95% CI)	(41.9, 91.6)

Change in BMI 95th percentile after 52 weeks of setmelanotide treatment (BBS patients)

In pivotal patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean reduction in the BMI 95th percentile score of -17.30 from active-treatment baseline (Table 32); this shifted the mean from Class 3 (≥140% of the 95th percentile) to Class 2 (120% to <140% of the 95th percentile) obesity based on Kumar 2019.

Table 32 Change in BMI 95th percentile from baseline after 52 weeks of setmelanotide treatment in BBS patients aged <18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic	Result
Percentage of the BMI 95th percentile score at ATB	N	16
	Mean (SD)	144.47 (35.806)
	Median (range)	139.24 (94.9, 239.8)
Percentage of the BMI 95th percentile score at Week 52	N	14
	Mean (SD)	126.82 (37.059)
	Median (range)	120.24 (74.2, 216.7)
Change after 52 weeks	N	14
	Mean (SD)	-17.30 (7.674)
	Median (range)	19.45 (-28.7, -6.4)
	95% CI	-21.73, -12.87
	p-value	<0.0001

Change in BMI after 52 weeks of setmelanotide treatment (BBS patients)

In pivotal patients aged ≥18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean BMI change from active-treatment baseline of -4.22 kg/m^2

and a mean percent change of -9.09%. In pivotal patients aged <18 years, 52 weeks of setmelanotide treatment resulted in a statistically significant mean reduction in BMI from active-treatment baseline of -3.36 kg/m^2 and -9.50% (Table 33).

Table 33 Change in BMI from baseline after 52 weeks of setmelanotide treatment in BBS patients aged <18 years or aged ≥18 years (Study RM-493-023, pivotal patient FAS)

Parameter	Statistic [1]	<18 years	≥18 years
BMI at ATB (kg/m^2)	N	16	15
	Mean (SD)	37.44 (9.439)	46.35 (5.857)
	Median (range)	36.62 (24.4, 61.3)	46.22 (39.2, 57.8)
Change after 52 weeks (kg/m^2)	N	14	12
	Mean (SD)	-3.36 (2.070)	-4.22 (3.335)
	Median (range)	-3.56 (-6.9, 0.0)	-4.62 (-8.4, 3.0)
	95% CI	-4.55, -2.16	-6.34, -2.10
	p-value	<0.0001	0.0005
Percent change after 52 weeks	N	14	12
	Mean (SD)	-9.50 (6.440)	-9.09 (6.760)
	Median (range)	-9.99 (-25.4, 0.1)	-9.90 (-17.6, 5.3)
	95% CI	-13.22, -5.78	-13.39, -4.80
	p-value	<0.0001	0.0003

[1] 95% CI and p-value based on Rubin's rule.

Figure 11 shows individual BBS patient data of percent change from baseline in BMI. [redacted] pivotal patients treated with setmelanotide for 52 weeks showed reductions from active-treatment baseline in percent change in BMI. All patients included in the figure (n=26) received setmelanotide over 52 weeks. Six patients in the pivotal cohort discontinued (see Table 16) and therefore did not receive 52 weeks of setmelanotide, and are not represented in the figure.

Figure 11 Waterfall plot of percent change in BMI from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal BBS patient FAS)

Blue bars - patients receiving setmelanotide throughout the trial; red bars - patients receiving setmelanotide from Week 14.

Post-hoc analysis of BMI/BMI Z-score category shifts (BBS patients)

Post-hoc analysis of shift in BMI class for the adult pivotal patients who were classified as responders to setmelanotide (n=7) showed that [redacted] adult patients had a decrease of [redacted] BMI class level (Table 34). In clinical practice, patients who do not respond adequately will discontinue setmelanotide treatment and so they were not included in this analysis, which was used to inform on the economic model.

Table 34 BMI shift data for individual BBS patients aged ≥18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients)

Obesity class	BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50+	[redacted]						
IV	45 to <50							
III	40 to <45							
II	35 to <40							
I	30 to < 35							
Over weight	25 to <30							
Class change								

Light grey shading = baseline value; dark grey shading = end of study value

A similar post-hoc analysis of shift in BMI Z-score class for the 12 pivotal paediatric patients who responded to setmelanotide (Table 35) showed that [redacted] had a decrease of [redacted] BMI class levels. The average shift for paediatric patients who were defined as responders was a decrease of [redacted] BMI Z-score class.

Table 35 BMI Z-score shift data for individual BBS patients aged <18 years who were classified as 52-week responders (Study RM-493-023, pivotal patients)

BMI Z-score	[redacted]
4+	
3.5 to <4	
3 to <3.5	
2.5 to <3	
2 to <2.5	
1 to <2	
<1	
Class change	

Light grey shading = baseline value; dark grey shading = end of study value

B.2.6.1.4 Measures of body composition

Measures of body composition showed that the weight loss seen over 52 weeks was due to loss of fat. Over 52 weeks of treatment BBS patients aged ≥6 years treated with setmelanotide saw:

- Mean body fat loss of 5.6 kg (11.3%) whilst lean muscle remained relatively stable with a loss of 1.2 kg (2.0%).
- Mean waist circumference decreased by 7.2 cm (6.3%).
- Low-density lipoprotein cholesterol level reduced by 7.8% and high-density lipoprotein cholesterol increased by 5.3%; total cholesterol was reduced by 6.1% and triglycerides by 9.6%.

Body fat and lean muscle mass

In pivotal BBS patients of all ages (≥6 years), treatment with setmelanotide for 52 weeks resulted in loss of body fat whilst lean muscle mass was minimally reduced (Table 36).

Table 36 Change in body fat and lean muscle mass from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal BBS patients)

Parameter	Statistic	Body fat	Lean muscle mass
ATB (kg)	N	29	29
	Mean (SD)	51.1 (18.9)	58.9 (14.1)
Change after 52 weeks (kg)	N	18	18
	Mean (SD)	-5.6 (12.0)	-1.2 (3.9)
Percent change after 52 weeks	N	18	18
	Mean (SD)	-11.3 (26.3)	-2.0 (6.5)

Waist circumference

In pivotal BBS patients of all ages, 52 weeks of setmelanotide treatment resulted in a mean reduction in waist circumference from active-treatment baseline of 7.18 cm (Table 37).

Table 37 Change in waist circumference from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal BBS patient FAS)

Parameter	Statistic	Result
Waist circumference at ATB (cm)	N	31
	Mean (SD)	117.89 (18.022)
	Median (range)	122.00 (79.7, 156.2)
Change after 52 weeks (cm)	N	25
	Mean (SD)	-7.18 (7.402)
	Median (range)	-6.20 (-25.1, 7.9)
	95% CI	-10.236, -4.124
Percent change after 52 weeks	N	25
	Mean (SD)	-6.33 (7.411)
	Median (range)	-4.31 (-26.7, 9.9)
	95% CI	-9.391, -3.273

Lipid profile

In BBS patients of all ages, 52 weeks of setmelanotide treatment reduced total cholesterol, low-density lipoprotein, and triglyceride levels and increased high-density lipoprotein levels (Table 38).

Table 38 Change in lipid profile from baseline after 52 weeks of setmelanotide treatment (Study RM-493-023, pivotal BBS patient FAS)

Parameter	Statistic	Total cholesterol (mmol/L)	High-density lipoprotein (mmol/L)	Low-density lipoprotein (mmol/L)	Triglycerides (mmol/L)
ATB	N	31	31	31	31
	Mean (SD)	4.39 (1.027)	1.08 (0.193)	2.99 (1.014)	1.86 (0.920)
	Median (range)	4.20 (2.6, 7.1)	1.00 (0.8, 1.6)	2.90 (1.5, 6.3)	1.62 (0.5, 4.4)
Change after 52 weeks	N	23	23	23	23
	Mean (SD)	-0.27 (0.437)	0.06 (0.137)	-0.21 (0.436)	-0.22 (0.620)
	Median (range)	-0.30 (-1.1, 0.7)	0.00 (-0.2, 0.4)	-0.30 (-1.0, 0.9)	-0.16 (-1.4, 1.3)
Percent change after 52 weeks	N	23	23	23	23
	Mean (SD)	-6.09 (10.566)	5.30 (11.561)	-7.82 (16.775)	-9.62 (32.543)
	Median (range)	-8.11 (-22.6, 19.2)	0.00 (-14.3, 30.8)	-10.26 (-33.3, 33.3)	-18.37 (-69.9, 67.2)

B.2.6.1.5 Quality of life in Study RM-493-023

After 52 weeks of treatment with setmelanotide, most patients reported improvements in or maintained their non-impaired quality of life.

IWQOL-Lite score

In pivotal BBS patients aged ≥18 years without cognitive impairment and providing data at active-treatment baseline and Week 52 (n = 11), the mean IWQOL-Lite total score at baseline was 74.9 (Table 39). This score falls within the moderate range of impairment (71.9 to 79.4) and is much lower than that seen in comparative non-obese populations in which a score of 94.7 (SD 7.6) would be expected (Crosby 2004). Treatment with setmelanotide for 52 weeks resulted in a +12-point mean improvement in IWQOL-Lite total score, which is equal to or greater than the threshold of 7.7 to 12 points (depending on baseline score) needed to demonstrate clinically-meaningful improvement on this scale (Crosby 2004).

At the individual patient level, 8 adults (72.7%) had HRQoL impairment at active-treatment baseline (mean 68.8; range 59.0 to 78.0), while the other 3 adults had non-impaired HRQoL. Of the 8 patients with HRQoL impairment at active-treatment baseline, 5 patients (62.5%) experienced clinically-meaningful improvement in IWQOL-Lite score after 52 weeks of treatment and the other 3 patients maintained their HRQoL. The mean change from active-treatment baseline in the 8 patients was +14.5 points, which is greater than the threshold of 7.7 to 12 points (depending on baseline score) needed to demonstrate clinically-meaningful improvement (Crosby 2004). The greatest mean improvements on IWQOL-Lite related to physical function and public distress subscales (Table 39).

Table 39 Effect of setmelanotide on IWQOL-Lite score in BBS patients aged ≥18 years without cognitive impairment and providing baseline and Week-52 data (Study RM-493-023, pivotal patients)

	Active-treatment baseline (n = 11)	Change from baseline to Week 52 (n = 11)
IWQOL-Lite total score, mean (SD)	**74.9 (12.6)**	**+12.0 (10.8)**
IWOQOL-Lite physical function score, mean (SD)	63.0 (13.9)	+15.3 (12.1)
IWOQOL-Lite sexual life score, mean (SD)	90.1 (14.9)	+9.3 (14.1)
IWOQOL-Lite work score, mean (SD)	83.7 (17.0)	+9.5 (14.7)
IWOQOL-Lite public distress score, mean (SD)	75.0 (20.0)	+12.7 (15.7)
IWOQOL-Lite self-esteem score, mean (SD)	79.1 (20.0)	+11.1 (16.7)

PedsQL score

In pivotal BBS patients aged <18 years old without cognitive impairment and with data at active-treatment baseline and Week 52 (n = 9), mean PedsQL total score at baseline was 67.2 (Table 40). This score is below the threshold 68.2 points considered indicative of impairment and is lower than the 83.0 seen in comparative populations without obesity (Schwimmer 2003).

Treatment with setmelanotide for 52 weeks resulted in a mean +11.2 point improvement in PedsQL total score (Table 40), which exceeds the threshold of 4.4 points needed to demonstrate a clinically-meaningful improvement on this scale (Varni 2003). At the individual patient level, 4 paediatric patients (44.4%) had HRQoL impairment at active-treatment baseline, with a mean total score of 47.8 (SD 10.9), while the other 5 paediatric patients had non-impaired HRQoL. All 4 patients (100%) with HRQoL impairment at baseline experienced a clinically-meaningful improvement in PedsQL score after 52 weeks of setmelanotide treatment. The 5 children with no HRQoL impairment at baseline, maintained or improved their HRQoL status (2 with clinically-meaningful improvement; 3 with maintained HRQoL).

Table 40 Effect of setmelanotide on PedsQL score in BBS patients aged <18 years without cognitive impairment who provided baseline and Week-52 data (Study RM-493-023, pivotal patients)

	Active-treatment baseline (n = 9)	Change from baseline to Week 52 (n = 9)
PedsQL total score, mean (SD)	**67.2 (20.1)**	**+11.2 (14.4)**
PedsQL physical function score, mean (SD)	60.4 (29.8)	+14.0 (29.3)
PedsQL psychosocial score, mean (SD)	70.7 (17.3)	+9.3 (10.5)

EQ-5D-5L score

In pivotal BBS patients aged ≥16 years without cognitive impairment and with data at active-treatment baseline and Week 52, mean baseline EQ-5D-5L scores ranged from [redacted] to [redacted] across the 5 subscales assessed (Table 41). After 52 weeks of setmelanotide treatment, patients generally reported improvements (decreases) in EQ-5D-5L health state scores, with the greatest improvements seen in mobility and usual activities scores. The mean EQ-5D visual analogue scale (VAS) score at active-treatment baseline was [redacted], which is below general population norm (Szende 2014), with subsequent increases seen after 52 weeks of setmelanotide treatment indicating improved health state.

Table 41 Effect of setmelanotide on EQ-5D-5L score in BBS patients aged ≥16 years without cognitive impairment (Study RM-493-023, pivotal patients)

	Active-treatment baseline n=13	Change from baseline to Week 52 n=13
Mobility score, mean (SD)	[redacted]	[redacted]
Self-care score, mean (SD)	[redacted]	[redacted]
Usual activities score, mean (SD)	[redacted]	[redacted]
Pain/discomfort score, mean (SD)	[redacted]	[redacted]
Anxiety/depression score, mean (SD)	[redacted]	[redacted]
VAS, mean (SD)	[redacted]	[redacted]

Patient level summary data

The ability of continued setmelanotide to maintain clinically-meaningful improvements in weight, BMI, hunger score and quality of life is summarised on an individual-patient basis in Table 42 for BBS patients aged ≥18 years and in Table 43 for patients aged <18 years.

Table 42 Symptom improvement in patients with BBS aged ≥18 years after 52 weeks of setmelanotide treatment (Study RM-493-023)

Patient	Age at study entry	Time on study	Weight change (%)	Change in BMI (%)	Change in most/ worst hunger (%)	Quality of life improvement

Light grey shading = disease stabilisation; dark grey shading = clinically-meaningful improvement

Table 43 Symptom improvement in patients with BBS aged <18 years after 52 weeks of setmelanotide treatment (Study RM-493-023)

Patient	Age at study entry	Time on study	Change in BMI Z-score	Change in BMI 95th percentile	Quality of life improvement

Light grey shading = disease stabilisation; dark grey shading = clinically-meaningful improvement.

B.2.6.2 Study RM-493-022

Study RM-493-022 was a Phase 3 extension study for patients who completed 1 year of treatment in a prior setmelanotide trial (for BBS patients this was either Study RM-493-014 or RM-493-023). Study RM-493-022 provided up to 2 years of additional setmelanotide experience (36 months total time on setmelanotide). Time points listed in the results below refer to total time on setmelanotide treatment, rather than time in study RM-493-022.

A post-hoc analysis of responders entering Study RM-493-022 (defined as a patient who achieved ≥10% weight reduction [patients aged ≥18 years] or ≥0.3 BMI Z-score reduction [patients aged <18 years] after 1 year of setmelanotide treatment in their index trial) was carried out. Whilst a reduction of ≥0.2 in BMI Z-score is generally considered clinically significant and is the definition used in the economic analysis, for the purposes of this analysis a ≥0.3 BMI Z-score reduction was used to ensure that only patients who were clearly identifiable as responders were included.

Study RM-493-022 provided the following outcomes for use in the health economic model:

- Maintenance of effect among patients who initially responded to setmelanotide treatment.

B.2.6.2.1 BMI in Study RM-493-022 (BBS patients)

BBS patients who were considered setmelanotide responders and continued treatment in the extension study maintained their decrease in BMI over the duration of the extension study (Table 44). The mean percent change in BMI for the total population of responders (all age groups) at Month 36 (n=12) was [redacted]%, which compared favourably with the BMI change at Month 12 ([redacted]%; n=30). It is worth noting that the total population includes both adult and paediatric patients and that an increase in BMI is normal and expected as paediatric patients grow; for example, a boy on the 99.6th percentile for BMI would have a BMI of approximately 27 kg/m^2 at age 12; by age 15 his BMI would be expected to be 30 kg/m^2 (https://www.rcpch.ac.uk/sites/default/files/2018-03/boys_and_girls_bmi_chart.pdf). Similarly, a girl on the 99.6th percentile would be expected to see an increase from a BMI of approximately 28.5 kg/m^2 at age 12 to approximately 31 kg/m^2 at age 15.

Table 44 Change in BMI from baseline in setmelanotide responders of all ages (Study RM-493-022, BBS patients)

BMI at extension study timepoints	Statistic	Setmelanotide responders (N = 30)
Index study baseline (kg/m^2)	N	30
	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 12	N	[redacted]
Change after 12 months (kg/m^2)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 12 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 18	N	[redacted]
Change after 18 months (kg/m^2)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 18 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 24	N	[redacted]
Change after 24 months (kg/m^2)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 24 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 36	N	[redacted]
Change after 36 months (kg/m^2)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 36 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]

The proportion of responders who maintained ≥10% weight reduction from their index trial baseline comprised:

- [redacted] patients ([redacted]%) to Month 12
- [redacted] patients ([redacted]%) to Month 18
- [redacted] patients ([redacted]%) to Month 24
- and [redacted] patients ([redacted]%) to Month 36.

Note that not all patients had completed the full 36 months of treatment at the time of data reporting, hence the decrease in patient numbers seen at the timepoints above. Study RM-493-022 is currently ongoing and, to date, [redacted] of the original 30 responder patients have discontinued the study (Table 18).

B.2.6.2.2 Body weight in Study RM-493-022

Adult BBS patients who were considered setmelanotide responders and continued treatment in the extension study demonstrated the ability to maintain the significant and clinically-meaningful weight loss achieved after approximately 1 year of setmelanotide treatment in the index study (Table 45). Body weight data are only provided for the 11 adult responders, as reporting body weight was not considered appropriate for paediatric patients who are still growing and would therefore be expected to increase in weight over time. At data cut-off (June 2022), [redacted] of the [redacted] adult patients had received a total of 36 months of setmelanotide treatment. The mean percent change in body weight at Month 36 was [redacted]%, which compared favourably to the weight change at Month 12 ([redacted]%) despite the small sample size.

Table 45 Change in body weight from baseline in adult setmelanotide responders (Study RM-493-022, BBS patients)

Weight at extension study timepoints	Statistic	Adult setmelanotide responders (N = 11)
Index study baseline (kg)	N	[redacted]
	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 12	N	[redacted]
Change after 12 months (kg)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 12 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 18	N	[redacted]
Change after 18 months (kg)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 18 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 24	N	[redacted]
Change after 24 months (kg)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 24 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 36	N	[redacted]
Change after 36 months (kg)	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Percent change after 36 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]

The proportion of adult responders who maintained ≥10% weight reduction from the index trial baseline comprised:

- [redacted] patients ([redacted]%) to Month 12

- [redacted] patients ([redacted]%) to Month 18
- [redacted] patients ([redacted]%) to Month 24
- and [redacted] patients ([redacted]%) to Month 36.

B.2.6.2.3 BMI Z-score in paediatric patients

For paediatric responders, BMI Z-score is considered a more appropriate way of characterising obesity than change in body weight. BBS patients aged <18 years who were considered setmelanotide responders and continued treatment in the extension study maintained their decrease in BMI Z-score achieved after approximately 1 year of setmelanotide treatment in the index study (Table 46). The mean change in BMI Z-score at Month 36 was [redacted], compared with the earlier BMI Z-score change at Month 12 of [redacted].

Table 46 Change in BMI Z-score from baseline in setmelanotide responders aged <18 years (Study RM-493-022, BBS patients)

BMI Z-score at extension study timepoints	Statistic	Paediatric setmelanotide responders (N = 19)
Index study baseline	N	[redacted]
	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 12	N	[redacted]
Change after 12 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 18	N	[redacted]
Change after 18 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 24	N	[redacted]
Change after 24 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]
Month 36	N	[redacted]
Change after 36 months	Mean (SD)	[redacted]
	90% CI	[redacted]
	Median (range)	[redacted]

The proportion of paediatric responders who maintained ≥0.3 BMI Z-score reduction from the index trial baseline comprised:

- [redacted] patients ([redacted]%) to Month 12
- [redacted] patients ([redacted]%) to Month 18
- [redacted] patients ([redacted]%) to Month 24
- and [redacted] patients ([redacted]%) to Month 36.

B.2.6.2.4 Weight related results beyond 3 years of treatment in study RM-493-022

Table 47 summarises patient-level weight-related changes in Week 52 responders who received setmelanotide for longer than 3 years. Most patients who responded at 1 year continued to have pronounced reductions in weight-related parameters after longer-term treatment. The longest time on treatment was 5 years, with a corresponding -7.1% change in BMI.

Table 47 Change in weight-related parameters in Week 52 responders treated with setmelanotide for >3 years (Study RM-493-022, BBS patients)

Patient	Index trial baseline age / sex / race	Parameter	Index trial baseline	Month 12 and last available timepoint	Change from index trial baseline
[redacted]	[redacted]	BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	[redacted]
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%

Patient	Index trial baseline age / sex / race	Parameter	Index trial baseline	Month 12 and last available timepoint	Change from index trial baseline
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	[redacted]
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
[redacted]	[redacted]	BMI Z-score	[redacted]	Month 12	[redacted]
				[redacted]	
		BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		Weight (kg)	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%
		95th BMI	[redacted]	Month 12	[redacted]%
				[redacted]	[redacted]%

Four of the 30 patients in this analysis had BMI increases over baseline at Month 18, Month 24, or Month 36 but two of them were younger than 18 years. As noted earlier, BMI Z-score and 95th BMI are generally accepted as more accurate parameters than BMI for measuring weight response in paediatric patients, and these two patients still exhibited successful long-term weight maintenance when BMI Z-score and 95th BMI data were examined (Table 48). Thus, for [redacted] patients, weight-related changes tended to improve or stabilise over 3 years or longer. Natural history studies have shown that patients with BBS usually continue to gain weight over time; therefore, even stabilisation of weight loss or weight maintenance in BBS is beneficial.

Table 48 Paediatric patients with BMI increases over baseline (Study RM-493-022, BBS patients)

Patient	Index trial baseline age / sex / race	Weight-related parameter	Index trial baseline	On-treatment time point	Change from index trial baseline
[redacted]	[redacted]	BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				Month 18	[redacted]%
				Month 24	[redacted]%
				Month 36	[redacted]%
		BMI Z-score	[redacted]	Month 12	[redacted]
				Month 18	[redacted]
				Month 24	[redacted]
				Month 36	[redacted]
		95th BMI	[redacted]	Month 12	[redacted]
				Month 18	[redacted]
				Month 24	[redacted]
				Month 36	[redacted]
[redacted]	[redacted]	BMI (kg/m^2)	[redacted]	Month 12	[redacted]%
				Month 18	[redacted]%
				Month 24	[redacted]%
				Month 36	[redacted]%
		BMI Z-score	[redacted]	Month 12	[redacted]
				Month 18	[redacted]
				Month 24	[redacted]
				Month 36	[redacted]
		95th BMI	[redacted]	Month 12	[redacted]%
				Month 18	[redacted]%
				Month 24	[redacted]%
				Month 36	[redacted]%

B.2.7 Subgroup analysis

B.2.7.1 Patients with cognitive impairment

Many patients with BBS have a degree of cognitive impairment, and so it was considered important to evaluate the impact of cognitive status on the ability of setmelanotide to reduce body weight, BMI and hunger. Ad hoc analysis was conducted on data from Study RM-493-023 for this patient subgroup, with 95% CI and one-sided p-values estimated using Rubin's rule.

Setmelanotide treatment for 52 weeks resulted in statistically significant reductions in body weight from active-treatment baseline for pivotal patients aged ≥18 years irrespective of cognitive status (Appendix E, Table 1).

Similarly, 52 weeks of setmelanotide treatment resulted in reductions from active-treatment baseline in BMI Z-score in patients aged <18 years irrespective of cognitive status (Appendix E, Table 2). The reduction from baseline was statistically significant in patients with cognitive impairment but did not achieve statistical significance for the patients who did not have cognitive impairment due to the small sample size (n=4) and high degree of variability in this group.

Setmelanotide treatment over 52 weeks resulted in statistically significant reductions from active-treatment baseline in BMI, irrespective of cognitive status (Appendix E, Table 3).

In patients with cognitive impairment (of all ages), hunger was evaluated using the caregiver-completed PWS-FPD. As shown in Appendix E, Table 4, setmelanotide treatment over 52 weeks reduced mean hunger scores from active-treatment baseline.

A summary of the results for the subgroups is presented in Appendix E.

B.2.8 Meta-analysis

No meta-analyses have been conducted for this submission.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons have been conducted for this submission.

B.2.10 Adverse reactions

B.2.10.1 Study RM-493-023

All 44 BBS patients (100.0%) treated with setmelanotide in Study RM-493-023 were reported with at least 1 treatment-emergent adverse event (TEAE, Table 49);
3 patients (6.8%) were reported with a serious adverse event (SAE) during the study, none of which were considered setmelanotide related. Three patients were reported

with TEAEs leading to study drug withdrawal. There were no deaths during the study.

Table 49 Overview of treatment-emergent adverse events in all BBS patients (Study RM-493-023, pivotal and supplemental patient SAS)

Events, n (%)	Double-blind placebo-controlled period		Full study
	Setmelanotide (N=22)	Placebo (N=22)	N=44
TEAEs	21 (95.5)	21 (95.5)	44 (100.0)
Serious TEAEs	1 (4.5)	2 (9.1)	3 (6.8)
Serious treatment-related TEAEs	0 (0.0)	1 (4.5)	1 (2.3)
TEAEs leading to study drug withdrawal	0 (0.0)	2 (9.1)	3(6.8)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)

During the placebo-controlled period of Study RM-493-023, skin hyperpigmentation was the most notable TEAE and was only reported in patients who received setmelanotide ([redacted] patients, [redacted]%). A number of commonly reported TEAEs were associated with the study drug administration site, the most frequent being injection site erythema ([redacted] patients, [redacted]%). Other commonly reported TEAEs (Table 50) comprised skin hyperpigmentation ([redacted] patients, [redacted]%), nausea ([redacted] patients, [redacted]%) and vomiting ([redacted] patients, [redacted]%). All cases of nausea and vomiting were mild or moderate in severity, and none were serious; these events were infrequent after the first month of setmelanotide treatment.

Table 50 Treatment-emergent adverse events in all BBS patients (Study RM-493-023, pivotal and supplemental patient SAS)

	Double-blind placebo-controlled period		Full study N=44
	Setmelanotide (N=22)	Placebo (N=22)	
TEAEs, n (%)	21 (95.5)	21 (95.5)	[redacted]
Skin hyperpigmentation	13 (59.1)	0 (0.0)	[redacted]
Injection site erythema	10 (45.5)	11 (50.0)	[redacted]
Injection site pruritus	7 (31.8)	9 (40.9)	[redacted]
Injection site bruising	6 (27.3)	9 (40.9)	[redacted]
Nausea	5 (22.7)	6 (27.3)	[redacted]
Injection site pain	3 (13.6)	7 (31.8)	[redacted]
Vomiting	6 (27.3)	0 (0.0)	[redacted]
Injection site induration	5 (22.7)	4 (18.2)	[redacted]
Diarrhoea	2 (9.1)	1 (4.5)	[redacted]
Headache	5 (22.7)	7 (31.8)	[redacted]
Injection site oedema	2 (9.1)	1 (4.5)	[redacted]
Melanocytic nevus	1 (4.5)	0 (0.0)	[redacted]
Injection site haemorrhage	3 (13.6)	2 (9.1)	[redacted]
Spontaneous penile erection	1 (4.5)	0 (0.0)	[redacted]
Fatigue	0 (0.0)	2 (9.1)	[redacted]

Three patients experienced a total of 5 SAEs comprising:

- Anaphylactic reaction in a patient receiving placebo that was considered treatment related; the SAE resolved without sequelae following hospitalisation and medication.
- Anaemia that was considered not setmelanotide related (described as related to gynaecologic bleeding) and resolved without sequelae following hospitalisation, medication, and a medical procedure; the patient discontinued the study.
- Blindness while a patient was taking placebo. Neurological and orbital imaging/angiography were normal, as was pupillary response; there was a possible component of non-organic functional loss in a setting of a known history of hereditary retinal dystrophy due to BBS and the blindness did not resolve. The patient subsequently had an SAE of suicidal ideation, having verbalised suicidal ideation to friends; the C-SSRS showed that the patient was having daily suicidal thoughts and was given a crisis hotline number (which was not called). The SAE of suicidal ideation was reported as resolved but recurred approximately 1 month

later; the second event was subsequently reported as resolved. The SAEs of suicidal ideation were considered unrelated to setmelanotide and resolved without changing study medication.

TEAEs led to study drug withdrawal in 3 patients: the patient with anaphylaxis (while receiving placebo); 1 patient with hot flashes, nausea, headaches, vomiting, and abdominal pain; and 1 patient with nausea and vomiting.

No TEAEs led to death during the study.

No clinically-meaningful changes in blood pressure or heart rate were observed during setmelanotide treatment.

B.2.10.2 Study RM-493-022

All 30 BBS patients (100.0%) who were considered setmelanotide responders and treated with setmelanotide in Study RM-493-022 were reported with at least 1 TEAE during treatment with setmelanotide (in both the index trial and Study RM-493-022, Table 51); 3 patients (10.0%) were reported with an SAE during the study, none of which were considered setmelanotide related. One patient was reported with a TEAE leading to study drug withdrawal. There were no deaths during the study.

Table 51 Overview of treatment-emergent adverse events for BBS patients considered setmelanotide responders (Study RM-493-022 and the index trial)

Events, n (%)	Setmelanotide responders N=30
TEAEs	[redacted]
Treatment-related TEAEs	[redacted]
Serious TEAEs	[redacted]
Serious treatment-related TEAEs	[redacted]
TEAEs leading to study drug discontinuation	[redacted]
TEAEs leading to death	[redacted]

Injection site reactions, skin hyperpigmentation, and nausea were observed in at least a third of the patients throughout the duration of exposure to setmelanotide from the start of the index trial (Table 52).

Table 52 Common (≥30% of patients) treatment-emergent adverse events in BBS patients considered setmelanotide responders (Study RM-493-022 and the index trial)

	Setmelanotide responders N=30
TEAEs, n (%)	[redacted]
Injection site pruritus	[redacted]
Injection site erythema	[redacted]
Skin hyperpigmentation	[redacted]
Injection site bruising	[redacted]
Injection site induration	[redacted]
Injection site pain	[redacted]
Injection site oedema	[redacted]
Nausea	[redacted]

Appendix F provides details of studies that report additional adverse reactions to those reported in studies in Section 2.2.

B.2.11 Ongoing studies

There are no ongoing studies.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Principal findings

Setmelanotide is a clinically-effective treatment for hyperphagia and obesity in patients with BBS demonstrating clinically relevant reductions in hunger (a component of hyperphagia, which is a hallmark of BBS related obesity with significant impact on patient quality of life) and weight. During the 14-week placebo-controlled treatment period in Phase 3 Study RM-493-023, patients receiving setmelanotide consistently showed greater reduction in hunger (a mean decrease of [redacted]% in hunger score compared with [redacted]% for those receiving placebo), body weight (-5.52 kg vs [redacted] kg with placebo, p=0.0079) and BMI ([redacted] kg/m^2 vs [redacted] kg/m^2 with placebo, p=0.0002). The reductions in body weight and BMI are assumed to be due to reductions in hunger and hyperphagia following setmelanotide treatment.

Over 52 weeks of treatment, reductions in hunger and weight loss were sustained. Setmelanotide resulted in a 30.9% reduction in maximal hunger score and clinically - meaningful and statistically significant reductions in body weight (a median 8.13 kg reduction in patients aged ≥18 years) and weight-related parameters (a 3.23kg/m^2 reduction in BMI; a reduction of 0.77 in BMI Z-score, a reduction of 17.30 in BMI 95th percentile) in adult and paediatric patients with BBS and obesity. Numerical improvements in health-related quality of life (an increase of 12 in IWQOL-Lite score), waist circumference (a reduction of 7.18 cm), and lipid profile (a 6.1% reduction in total cholesterol; a 7.8% reduction in low-density lipoprotein; a 9.6% reduction in triglycerides) were also seen.

A long-term extension study providing up to 2 years of additional setmelanotide treatment experience (3 years total experience) in patients who were deemed to have responded to setmelanotide in their index trial, showed that the treatment effect on weight-related parameters was maintained over the long-term. The mean percent change in BMI for responders across age groups at Month 36 was [redacted]%, which compared favourably with BMI change at Month 12 ([redacted]%).

The safety and tolerability profile of setmelanotide in patients with BBS was consistent with that observed in other clinical trials with setmelanotide in patients with other rare genetic diseases of obesity; no new safety concerns were observed. The main AEs were skin hyperpigmentation, injection site reactions and nausea.

External validity

The BBS patient populations included in the clinical trials described in this document are reflective of the population that would be eligible for setmelanotide treatment; clinical trials only included patients with a BMI ≥30 kg/m^2, which is the population that would be eligible in clinical practice. In addition, the data presented for the long-term extension trial (RM-493-022) only includes patients who were considered ‘responders’ in their index trial i.e. adult patients who had achieved ≥10% weight reduction and paediatric patients who had achieved ≥0.3 BMI Z-score reduction after 1 year of setmelanotide treatment in their index trial. In clinical practice it is likely that any patients not meeting these thresholds would not continue to receive

setmelanotide treatment in the long-term; however it is acknowledged that in clinical practice a reduction of ≥0.2 in BMI Z-score may be considered a response.

Hyperphagia is a complex condition consisting of an interplay between hunger, satiety and a preoccupation with food which combine to result in obesity. Hyperphagia can be classified as mild, moderate and severe. With mild hyperphagia, patients may sometimes overeat to the point of discomfort and sometimes fail to feel full after eating a normally-sized meal; occasionally they will try to sneak food and eat when they wake at night. Severe hyperphagia, on the other hand, is described as: almost never feeling full after a normally-sized meal; overeating to the point of discomfort at most meals; trying to sneak food almost every day; and eating at night most nights. Whilst the focus of this submission is patients with severe hyperphagia, severe hyperphagia was not specified as an inclusion criterion for either of the setmelanotide clinical trials discussed in this submission; in addition, the trials did not include a direct measure of hyperphagia severity. However, hyperphagia is the underlying cause of obesity in BBS patients, with impairment of the MC4R pathway leading to excessive hunger and lack of satiety so that patients consuming more calories than needed to maintain a healthy weight. All patients in the trials had a BMI of ≥30 kg/m^2, suggesting that all were suffering from severe hyperphagia. In order to see a weight response to setmelanotide, patients must first experience a reduction in hyperphagia. It is therefore assumed that patients who responded to setmelanotide (i.e. adults who achieved ≥10% weight reduction and paediatric patients who achieved ≥0.2 BMI Z-score reduction) must also have experienced a significant reduction in their hyperphagia levels, sufficient to classify their on-treatment hyperphagia as mild.

The quality-of-life values reported in study RM-493-023 indicate that patients with BBS have a quality of life slightly below population norms, which seems at odds with a disease whose manifestations can include obesity, hyperphagia, vision loss, undeveloped genitals and kidney failure. It is therefore apparent that these quality-of-life scores do not accurately reflect the lived experience of BBS patients. It has previously been suggested that EQ5D does not fully capture the impact of sensory impairment on quality of life (Perneger 2011), and this may also be true for hyperphagia, and may explain the differences between how patients describe the

impact of their condition and the EQ5D values reported in this study. The main factor contributing to decreased quality of life is hyperphagia which manifests as increased food intake, impaired satiety, an intense preoccupation with food and excessive food-seeking behaviour resulting in psychological stress and social isolation (Zorn 2022). In addition, patients with hyperphagia and BBS have experienced hyperphagia since infancy; hence they are probably unaware of what it feels like to not be burdened by constant feelings of hunger and food seeking behaviours or the impact these feelings have on their daily lives. It is also psychologically self-preserving that patients who have never experienced good health are inclined to find their life more bearable than it might appear to a 'healthy' onlooker. This theory is supported by the results of a vignette study (Appendix O) conducted by Rhythm Pharmaceuticals that asked members of the general population in England and Scotland to value four hypothetical health states related to no hyperphagia, mild, moderate and severe hyperphagia. When presented with a description of severe hyperphagia, data from 215 participants resulted in a utility value of [redacted] when analysed using an accepted methodology whereby derived utility values of less than 0 were set to 0. Participants stated that the key factors in their decision were the emotional distress, impact on daily activities, the idea of never feeling full, and the impact on family and social relationships. If BBS patients have never experienced being able to complete the daily activities that the general population takes for granted, it is unlikely that they would be able to fully assess the impact of their condition on these activities. This theory is supported by a series of exit interviews conducted by Rhythm Pharmaceuticals to gain a more accurate picture of hunger levels in BBS patients. Patients who had participated in a setmelanotide trial were asked to rate their hunger before treatment and during the clinical trial. The 8 patients who provided ratings, gave an average highest pre-treatment hunger score of 8.8 (range 8 to 10) and a highest hunger score during the clinical trial of 4.1 (range 2 to 6). Lowest pre-treatment hunger ratings before retrospectively described as a mean of 4.3 (range 2 to 6), with the most patients (6 of 8) never having experiencing a time before setmelanotide treatment when they were not hungry (denoted by a score of 0). During the clinical trial, lowest hunger averaged 0.7 (range 0 to 2), with only 2 patients not experiencing a 0 hunger rating.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Appendix G describes the methods and results used to identify published cost-effectiveness analyses relevant to the technology evaluation.

An SLR was conducted to synthesise the evidence on epidemiology outcomes, clinical outcomes, and the humanistic and economic burden of obesity in patients diagnosed with BBS. No studies were identified by the SLR that considered: costs or medical resource use associated with management of obesity in patients with BBS; or the cost-effectiveness of interventions to treat obesity in patients with BBS. There were also no published cost-effectiveness studies relating to setmelanotide. No other published cost-effectiveness studies were identified that were relevant to the technology evaluation.

B.3.2 Economic analysis

No economic analyses of the cost-effectiveness of treatments for patients with BBS and hyperphagia and obesity were identified by the SLR. The model structure was, therefore, based on previously developed cost-effectiveness models used in NICE submissions which were identified by hand searching. Each submission and the relevant contribution to the model is described:

- A Markov state-transition cohort model was used in the liraglutide submission (TA664, NICE 2020a) to model changes in the BMI trajectories of treated patients. In this model, patient BMI drove the risk of obesity-related comorbidities including sleep apnoea, T2DM, cardiovascular events, and cancer.
- The naltrexone-bupropion submission (TA494, NICE 2017) for overweight and obese patients used a patient-simulation approach in Excel® with a condition-event methodology.
- A Markov model and patient-level approach were implemented using discrete-event simulation in the rimonabant (TA144, NICE 2008) submission.
- The recent setmelanotide submission for treatment of obesity caused by a deficiency in LEPR or POMC (HST21, NICE 2022) was heavily relied upon for

many modelling traits including the underlying life-table model, the influence of BMI on obesity-related comorbidity probabilities, and the approach to modelling hyperphagia.

B.3.2.1 Patient population

The analysis considered adult or paediatric patients with BBS, aged ≥6 years who had severe hyperphagia and obesity; this aligns with a sub-population of the licensed indication for setmelanotide. Baseline characteristics of the modelled cohort were based on evidence from a pivotal Phase 3 trial of patients with BBS aged ≥6 years (Study RM-493-023, NCT03746522, Section B.2.3.3). Base-case model results presented for the paediatric population assumed that treatment started at the age of 6 years, as per the target population for setmelanotide. Currently treatment initiation in the BBS population includes adults; in the future it is expected that BBS patients with hyperphagia and obesity will start setmelanotide treatment as children with the aim of reducing or preventing the long-term consequences of childhood obesity on other aspects of health and on mental well-being.

B.3.2.2 Model structure

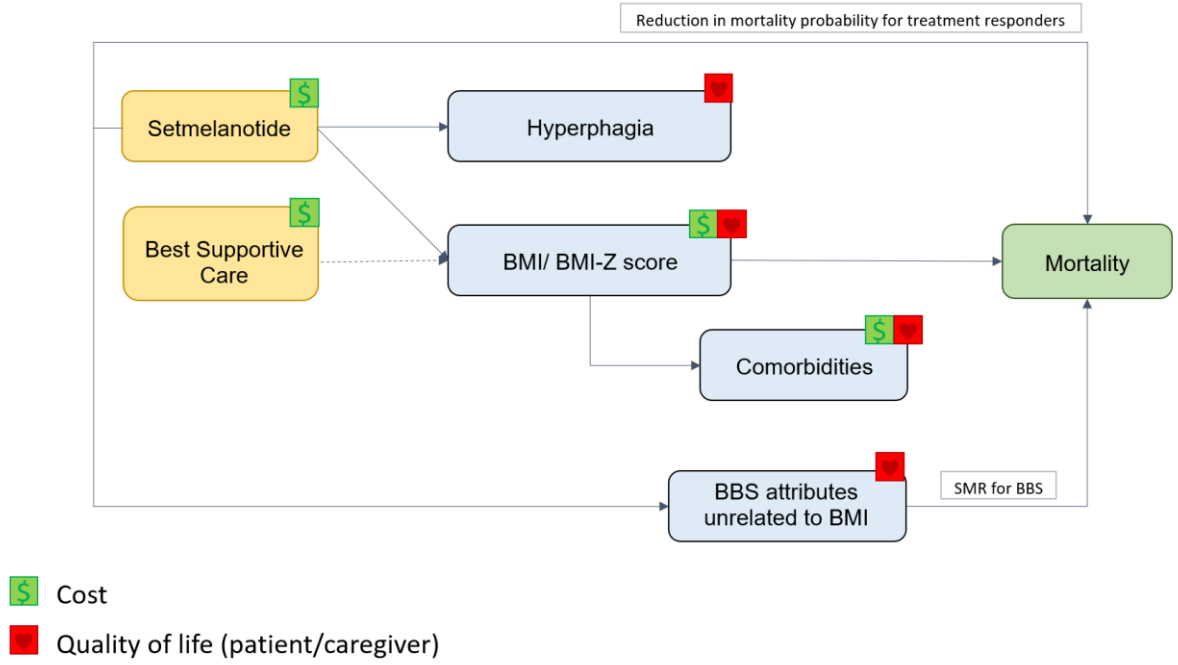
The cost-effectiveness analysis used a lifetime model based on UK life tables. Model disease 'states' comprised seven BMI/BMI Z-score categories along with a 'death' state for both the setmelanotide and BSC arms. Treatment with setmelanotide was assumed to alter the distribution of patients across BMI/BMI Z-score categories, with higher BMI/BMI Z-score assumed to be associated with a higher mortality risk based on BMI category risk ratios taken from the literature. Once patients discontinued setmelanotide they reverted to their original BMI/BMI Z-score category in the BSC arm. The model evaluated yearly 'cycles' and half-cycle correction was implemented.

The model considered the costs of treating obesity in patients with BBS, the medical costs and HRQoL impact associated with increased BMI, the utility of living with hyperphagia, and the costs and utility decrements of obesity-related comorbidities, including sleep apnoea, osteoarthritis, NASH, T2DM, and cardiovascular events.

A conceptual diagram showing model drivers is presented in Figure 12. Patients in the model were treated with setmelanotide in addition to BSC or received BSC alone (Section **B.3.2.3**). Although BSC may impact patient BMI/BMI Z-score, setmelanotide

also manages the BBS patient's hyperphagia which has a major influence on health; the severity of hyperphagia affects patient quality of life, with severe hyperphagia corresponding to lower utility values. BMI/BMI Z-score categories are associated with annual patient healthcare resource use, quantified as direct medical costs and obesity-related quality of life scores; BMI/BMI Z-score category also drives mortality risk with an associated standardised mortality ratio (SMR) for BMI/BMI Z-scores above normal, and obesity-related comorbidities are also associated with costs and disutilities.

Figure 12 Drivers of the cost-effectiveness model of setmelanotide treatment of BBS patients



The model accounts for three different hyperphagia levels (mild, moderate, and severe) that are associated with unique utility multipliers. Similarly, BMI and BMI Z-score are each stratified into seven categories:

- For paediatric patients BMI Z-score categories were defined as: BMI Z-score 0.0-<1.0; BMI Z-score 1.0 to <2.0; BMI Z-score 2.0 to <2.5; BMI Z-score 2.5 to <3.0; BMI Z-score 3.0 to <3.5; BMI Z-score 3.5 to <4.0; and BMI Z-score ≥4.0.
- Similarly, adult BMI categories comprised: BMI <25; BMI 25 to <30; BMI 30 to <35; BMI 35 to <40; BMI 40 to <45; BMI 45 to <50; and BMI ≥50.

Paediatric patients transitioned from their BMI Z-score category to the aligned BMI category at the age of 18 years, as shown in Table 53. The influence of treatment on

hyperphagia was modelled separately from that for BMI/BMI Z-score, so that both influenced quality of life independently.

Table 53 Methodology for mapping BMI Z-score to BMI

		BMI Z-score						
		0.0 to <1.0	1.0 to <2.0	2.0 to <2.5	2.5 to <3.0	3.0 to <3.5	3.5 to >4.0	≥4.0
BMI (kg/m^2)	20 to <25	100%	0%	0%	0%	0%	0%	0%
	25 to <30	0%	100%	0%	0%	0%	0%	0%
	30 to <35	0%	0%	100%	100%	0%	0%	0%
	35 to <40	0%	0%	0%	0%	100%	0%	0%
	40 to <45	0%	0%	0%	0%	0%	100%	33%
	45 to <50	0%	0%	0%	0%	0%	0%	33%
	≥50	0%	0%	0%	0%	0%	0%	33%

Mortality was modelled using UK life-table data for the general population which was then adjusted for obesity using SMRs corresponding to each BMI/BMI Z-score category. This captured an indirect treatment effect on mortality through change in BMI/BMI Z-score. Mortality effects from non-BMI-related aspects of BBS were applied multiplicatively as SMRs to the resulting mortality probabilities by BMI/BMI Z-score level, reflecting the higher risk of death for BBS patients compared with the general population and a reduction in mortality for patients treated with setmelanotide. Setmelanotide can further affect mortality probability by influencing the prevalence of comorbidities such as cardiovascular events, for which BBS patients have poorer outcomes than the general obese population. This was quantified in the model as an SMR of <1 to capture the mortality benefit gained by reducing the onset of BBS-related comorbidities.

While no NICE technology evaluations have been conducted previously for the BBS population, setmelanotide was recently recommended for treatment of obesity in patients with a LEPR or POMC deficiency (submission HST21, NICE 2022). This is a similarly unique and debilitating genetic condition that causes hyperphagia which, in turn, leads to obesity; since both conditions are rare, disease-specific data sources are scarce. Much of the same data used to populate the model for the LEPR/POMC submission were used here and were based on the general obese population as a proxy. Literature searches conducted for submission HST21 were updated and used

to populate the BBS model. Data derived from the general obese population included: mortality, cost, and utility values by BMI/BMI Z-score category; hyperphagia utility multipliers; comorbidity prevalence and decrements; and caregiver disutility. Both the BBS and LEPR/POMC models were built using similar assumptions including the comparator, time horizon, and overall modelling techniques (Table 54). The main deviation from the setmelanotide LEPR/POMC submission was that baseline and treatment-effect data in the BBS model used BBS clinical trial results, which ultimately drives model outcomes. The BBS model also included SMRs for BBS-related comorbidities, comprising early-onset obesity and each obesity-related comorbidity, which were not applied to the LEPR/POMC model.

Table 54 Features of the setmelanotide in BBS economic analysis

Factor	Previous evaluations	Chosen values	Justification
Time horizon	Lifetime [submission HST21]	Lifetime	A lifetime time horizon was chosen because of the life-long impact of BBS on affected patients, to allow all long-term health impacts to be accounted for. The NICE reference case requirement is that the time horizon be sufficient to reflect all important differences in costs or outcomes between technologies; as treatments extend throughout a patient's life, there are significant value drivers to be reflected over the entire lifetime.
Treatment waning effect	Not applied [submission HST21]	Assumed to be 0	Waning effects were not modelled in the LEPR/POMC population assessed in submission HST21 and were not included in this submission. The model includes long-term treatment for responders only. Lack of treatment effect would be apparent to patients, treating physicians and carers as a return to severe hyperphagia and at that point treatment would be discontinued.
Utilities	Various literature sources [submission HST21]	Various literature sources	The NICE reference case recommends that utility values be reported directly by patients or carers. An explanation for the deviation from the reference case is presented in Section B.3.4.1.
Costs	NHS reference list price and various literature sources [submission HST21]	NHS reference list price and various literature sources	The NICE reference case states that costs should relate to NHS and Personal Social Services (PSS) resources and be valued using prices relevant to the NHS and PSS. All literature used for pricing reflected UK costs and the UK patient cohort.

B.3.2.3 Intervention technology and comparators

The comparator used in the cost-effectiveness model is BSC, which is defined as lifestyle and dietary interventions and behavioural therapy. The regimen for patients with obesity with genetic mutations is assumed to be equivalent to that for the general obese population, as described in NICE guideline CG189 (NICE 2014).

Setmelanotide (IMCIVREE®), the intervention technology, is a selective melanocortin-4 receptor agonist for the control of hyperphagia and treatment of obesity associated with genetically-confirmed BBS in adult and paediatric patients

aged ≥6 years (Section B.1.2). Setmelanotide is not expected to displace the use of BSC in the UK population, rather it will be used in addition to BSC.

B.3.3 Clinical parameters and variables

B.3.3.1 Clinical inputs into the model

Patient characteristics for the model population were informed by baseline data from Study RM-493-023 (NCT03746522). This included the initial patient distribution for BMI Z-score categories (Table 13) and sex (Table 12). A hyperphagia severity parameter, stratified to low, moderate and high severity, served as an intermediate outcome that influenced patient quality-of-life score. BMI/BMI Z-score category was also an intermediate outcome that linked to quality of life and mortality, and drove comorbidity prevalence. Comorbidities were also associated with a quality-of-life impact and a cost.

B.3.3.2 Treatment effect

Setmelanotide treatment effects comprised improvements in BMI/BMI Z-score and hyperphagia score. The modelled treatment effect on BMI/BMI Z-score was quantified as the average number of BMI/BMI Z-score categories that treatment responders improved by, using 52-week clinical trial results, compared with baseline BMI/BMI Z-score categories (Table 34 and Table 35). Paediatric responders experienced a [redacted] decrease in BMI Z-score category.

A paediatric treatment responder was defined as a patient aged <18 years at baseline who achieved a BMI Z-score decrease of ≥0.2 from baseline to the 52-week endpoint based on clinical trial results. The response rate using this definition was 85.7% (Table 31).

Patients receiving BSC only were assumed to have no treatment response in terms of BMI/BMI Z-score, as previous evidence shows that BSC is an ineffective approach for managing genetic obesity. As impairment of the MC4R pathway is the root cause of hyperphagia and obesity in BBS patients, management with diet and exercise (BSC) has no impact on hyperphagia and as a consequence is unlikely to have a meaningful effect on obesity for this population.

The effect of setmelanotide on hyperphagia reflected that seen for BMI/BMI Z-score. Setmelanotide works on the root cause of BBS hyperphagia by activating melanocortin receptors in the brain, this reduces hyperphagia severity which in turn reduces the patient's need to eat with consequential reductions in weight and BMI/BMI Z-score. It could be expected that responding patients would have a significantly reduced hyperphagia level, as would be necessary to drive a clinically meaningful improvement in their BMI/BMI Z-score. It was, therefore, assumed that any patient with a setmelanotide treatment response experienced an improvement to a state of mild hyperphagia by the end of treatment. As hyperphagia severity was linked to quality of life in the model, through a severity-specific utility multiplier, these changes manifested as an increased hyperphagia utility for treatment responders compared with patients receiving BSC only.

Setmelanotide is well tolerated and discontinuation rates for patients responding to treatment are assumed to be very low. A discontinuation rate of 1% per year was used, as consistent with NICE submission HST21 for setmelanotide treatment in patients with obesity caused by LEPR/POMC deficiency (NICE 2022). Patients who discontinued treatment were assumed to revert back to their baseline BMI/BMI ZF-score category immediately, with no tapering of treatment effect.

Treatment waning was assumed to be negligible, as setmelanotide activates melanocortin receptors in the brain to restore MC4R pathway signalling to reduce hyperphagia. No long-term data are available to inform on the effect of treatment waning but this approach is consistent with that used in the submission for setmelanotide treatment in LEPR/POMC deficiency (NICE 2022).

B.3.3.3 Comorbidity prevalence

The prevalence of comorbidities relative to each BMI/BMI Z-score category was informed by the literature, as identified using a combination of approaches including an SLR for comorbidity prevalence in general obesity with focused data reviews to fill in gaps. Comorbidity prevalence data reflect those for the general obese population, given the lack of published data for BBS patients. This approach was previously used and accepted by NICE in the submission for setmelanotide treatment of patients with obesity caused by LEPR/POMC deficiency (NICE 2022).

The prevalence of sleep apnoea for each BMI category in the adult population is presented in Table 55. The reported prevalence of an apnoea-hypopnea index of ≥15 was used for BMI levels 20 to <25 kg/m^2 and 25 to <30 kg/m^2 (Young 2002). Prevalence for BMI categories 30 to <35 kg/m^2, 35 to <40 kg/m^2, 40 to<50 kg/m^2, and ≥50 kg/m^2 were taken from a study of morbidly obese patients who had undergone weight loss surgery (Lopez 2008); the estimate for patients with BMI of ≥50 kg/m^2 was calculated using the average of reported prevalence for the 50 to <60 kg/m^2 BMI category and the ≥60 kg/m^2 category.

Table 55 Sleep apnoea prevalence by BMI category

BMI	Prevalence	Reference
20 to <25 kg/m^2	10.00%	Young 2002
25 to <30 kg/m^2	15.00%	Young 2002
30 to <35 kg/m^2	33.33%	Lopez 2008
35 to <40 kg/m^2	71.43%	Lopez 2008
40 to <45 kg/m^2	73.48%	Lopez 2008
45 to <50 kg/m^2	73.48%	Lopez 2008
≥50 kg/m^2	85.75%	Lopez 2008

Prevalence inputs for osteoarthritis, T2DM, and cardiovascular events were taken from a cross-sectional survey of adults eligible for bariatric surgery in England (Ahmad 2014). The values and subgroups used for each input are detailed in Table ***56***; cardiovascular event values were calculated by summing the prevalence of stroke and coronary heart disease (CHD).

Table 56 BMI-based prevalence values for osteoarthritis and type 2 diabetes (Ahmad 2014)

BMI	Prevalence	Subgroup in source document
Osteoarthritis		
20 to <25 kg/m^2	6.10%	Lower CI of BMI <35 kg/m^2 group
25 to <30 kg/m^2	6.60%	Mean of BMI <35 kg/m^2 group
30 to <35 kg/m^2	10.40%	Average of upper CI of BMI <35 kg/m^2 group and lower CI of BMI 35 to 40 kg/m^2 group
35 to <40 kg/m^2	16.20%	Mean of BMI 35 to 40 kg/m^2 group
40 to <45 kg/m^2	17.00%	Average of upper CI of BMI 35 to 40 kg/m^2 group and lower CI of BMI >40 kg/m^2 group
45 to <50 kg/m^2	21.10%	Mean of BMI >40 kg/m^2 group
≥50 kg/m^2	26.90%	Upper CI of BMI >40 kg/m^2 group
Type 2 diabetes		
20 to <25 kg/m^2	2.80%	Lower CI of BMI <35 kg/m^2 group
25 to <30 kg/m^2	3.20%	Mean of BMI <35 kg/m^2 group
30 to <35 kg/m^2	5.20%	Average of upper CI of BMI <35 kg/m^2 group and lower CI of BMI 35 to 40 kg/m^2 group
35 to <40 kg/m^2	8.80%	Mean of BMI 35 to 40 kg/m^2 group
40 to <45 kg/m^2	10.85%	Average of upper CI of BMI 35 to 40 kg/m^2 group and lower CI of BMI >40 kg/m^2 group
45 to <50 kg/m^2	16.70%	Mean of BMI >40 kg/m^2 group
≥50 kg/m^2	22.50%	Upper CI of BMI >40 kg/m^2 group
Cardiovascular events (sum of the prevalence of stroke and CHD)		
20 to <25 kg/m^2	3.80%	Lower CI of BMI <35 kg/m^2 group
25 to <30 kg/m^2	4.40%	Mean of BMI <35 kg/m^2 group
30 to <35 kg/m^2	5.25%	Average of upper CI of BMI <35 kg/m^2 group and lower CI of BMI 35 to 40 kg/m^2 group
35 to <40 kg/m^2	8.30%	Mean of BMI 35 to 40 kg/m^2 group
40 to <45 kg/m^2	7.65%	Average of upper CI of BMI 35 to 40 kg/m^2 group and lower CI of BMI >40 kg/m^2 group
45 to <50 kg/m^2	10.50%	Mean of BMI >40 kg/m^2 group
≥50 kg/m^2	16.80%	Upper CI of BMI >40 kg/m^2 group

The proportions of each cardiovascular event assumed to occur within the event prevalence presented in Table 57 were used to calculate an average annual cost for these events, as described in Section B.3.5.2.

Table 57 Cardiovascular event proportions

Type of event	Proportion used in the model	Notes
Myocardial infarction	35.65%	Calculated as the proportion of initial myocardial infarction and sudden and non-sudden CHD of total CHD (excluding coronary insufficiency) in D'Agostino 2000 for males and females multiplied by the proportion of CHD (excluding coronary insufficiency) of total CHD plus stroke from D'Agostino 2008. An equal ratio of males and females was assumed
Angina	39.81%	Calculated as the proportion of initial angina of total CHD (excluding coronary insufficiency) in D'Agostino 2000 for males and females multiplied by the proportion of CHD (excluding coronary insufficiency) of total CHD plus stroke from D'Agostino 2008. An equal ratio of males and females was assumed
Stroke	21.67%	Calculated as the proportion of strokes of total CHD and strokes in D'Agostino 2008 multiplied by the proportion of strokes that are not transient ischemic attack from Wolf 1991 An equal ratio of males and females was assumed
Transient ischaemic attack	6.33%	Calculated as proportion of transient ischemic attack in total strokes from Wolf 1991 in males and females multiplied by the proportion of strokes in all CVD events. An equal ratio of males and females was assumed

The analysis assumed that all patients with NAFLD would progress to NASH, given the increased risk in the BBS population. The prevalence of NASH for lower BMI categories were based on NAFLD prevalence values from Estes 2018 for a UK population (Table 58). The prevalence values for BMI of ≥40 kg/m^2 were based on Mummadi 2008 estimates. Some BMI category values were linearly extrapolated from these data.

Table 58 BMI-based prevalence values for non-alcoholic steatohepatitis

BMI	Prevalence	Notes
Este 2018 (UK prevalence for all ages)		
20 to <25 kg/m^2	21.90%	
25 to <30 kg/m^2	43.45%	Linear extrapolation
30 to <35 kg/m^2	65.00%	Extrapolated to 65% and 75% to reach a mean of 70%
35 to <40 kg/m^2	75.00%	Extrapolated to 65% and 75% to reach a mean of 70%
Mummadi 2008		
40 to <45 kg/m^2	85.00%	Obese individuals
45 to <50 kg/m^2	90.00%	Linear extrapolation
≥50 kg/m^2	95.00%	Morbidly obese individuals

Comorbidity prevalence for paediatric patients aged <18 years were calculated using the values for bounding BMI categories (20 to <25 kg/m^2 and ≥50 kg/m^2) from the adult population for the lowest and highest BMI Z-score categories (0.0 to <1.0 and ≥4.0); a linear increase in prevalence with each BMI Z-score category was assumed. The resulting paediatric comorbidity prevalence values are shown in Table 59.

Table 59 Comorbidity prevalence for paediatric patients

BMI Z-score	Sleep apnoea	Osteoarthritis	NASH
0.0 to <1.0	4.50%	6.10%	21.90%
1.0 to <2.0	14.27%	9.57%	34.08%
2.0 to <2.5	24.04%	13.03%	46.27%
2.5 to <3.0	33.81%	16.50%	58.45%
3.0 to <3.5	43.58%	19.97%	70.63%
3.5 to <4.0	53.34%	23.43%	82.82%
≥4.0	63.11%	26.90%	95.00%

B.3.3.4 Mortality

No mortality data specific to the BBS population with obesity were identified by literature search. Mortality was, therefore, modelled using UK general population life tables, with SMRs by BMI informed by a population-based cohort study of 3.6 million UK adults (Bhaskaran 2018); additional SMRs by BMI/BMI Z-score were informed by a prospective cohort study of 41,359 Swedish individuals assessing the association of childhood obesity with mortality risk (Lindberg 2020). Treatment effect on mortality was estimated through impact on BMI/BMI Z-score, assuming a log-linear distribution of mortality across BMI Z-score categories; the mean SMR was calibrated to be equivalent to the total population SMR reported by Lindberg 2020,

using mean BMI Z-score and the aligning standard deviation. These SMRs were applied multiplicatively and resulted in the SMRs shown in Table 60. It was assumed that SMRs by BMI score would be equivalent to SMRs by BMI Z-score.

There is limited literature evidence relating to a direct mortality effect for setmelanotide, due to effects on non-obesity-related BBS symptoms not captured by SMR by BMI/BMI Z-score; however KOL opinion suggests that by impacting on comorbidities, such as cardiovascular events, it is plausible that there may be an unproven impact. We therefore assumed a mortality reduction of 15% for patients receiving setmelanotide by including an SMR of 0.85 while BBS patients were receiving setmelanotide treatment.

Table 60 Standardised mortality ratios by BMI/BMI Z-score for paediatric and adult patients with BBS (Bhaskaran 2018)

BMI (kg/m^2) / BMI Z-score	SMR by BMI	SMRs for early-onset obesity	Final SMR
20 to <25 / 0.0 to <1.0	1.00	1.00	1.00
25 to <30 / 1.0 to <2.0	1.21	1.99	2.41
30 to <35 / 2.0 to <2.5	1.46	2.36	3.46
35 to <40 / 2.5 to <3.0	1.77	2.80	4.97
40 to <45 / 3.0 to <3.5	2.14	3.33	7.14
45 to <50 / 3.5 to <4.0	2.59	3.96	10.26
≥50 / ≥4.0	3.14	4.70	14.74

B.3.4 Measurement and valuation of health effects

Health effects were captured as utility values and were expressed in quality-adjusted life years (QALYs), as recommended in the NICE reference case. Literature-based EQ-5D values were used to estimate HRQoL for BBS patients with obesity.

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was measured in BBS clinical trials using EQ-5D as per NICE guidance and as described in Section B.2.6.1.5. However, EQ-5D was not deemed to capture the impact of hyperphagia (the biggest driver of quality of life in BBS patients) on quality of life in the modelled population; these data were, therefore, considered inappropriate for use in the cost-effectiveness analysis (discussed in Section B.2.12).

B.3.4.2 Mapping

HRQoL data from clinical trials were not used in the cost-effectiveness model. Rather, health-utility data for hyperphagia were estimated using the vignette study detailed in Appendix O. HRQoL data for utility values by BMI Z-score in the paediatric population were mapped from PedsQL to EQ-5D using evidence from Riazi 2010 and the mapping algorithm presented by Khan 2014. Data from the early to post-pubertal subgroup with BMI Z-score averages of 3.5 (obese) and 0.3 (healthy) were used to populate the model BMI Z-score 0.0 to <1.0 and 3.5 to <4.0 category utility values, respectively. These values were mapped from PedsQL to EQ-5D using the ordinary least squares regression mapping algorithm shown in Table 61, and linear extrapolation was used to calculate utility values for the remaining BMI Z-score categories (Khan 2014).

Table 61 The ordinary least squares regression algorithm used to map BMI Z-score category utility values

	Ordinary least squares 5 coefficient	Obese group (mean BMI Z-score of 3.5)	Healthy control group (mean BMI Z-score of 0.3)
Constant	-0.428496	1.0	1.0
Physical functioning	0.009127	70.9	82.9
Emotional functioning	0.006611	66.5	73.2
Social functioning	0.005705	77.3	88.9
School functioning	0.006011	65.5	73.9
Physical functioning squared	0.000020	5026.8	6872.4
Emotional functioning squared	-0.000048	4422.3	5358.2
Social functioning squared	0.000011	5975.3	7903.2
School functioning squared	-0.000017	4290.3	5461.2
Physical functioning × emotional functioning	-0.000004	4714.9	6068.3
Physical functioning × social functioning	-0.000055	5480.6	7369.8
Physical functioning × school functioning	-0.000066	4644.0	6126.3
Emotional functioning × social functioning	-0.000009	5140.5	6507.5
Emotional functioning × school functioning	0.000059	4355.8	5409.5
Social functioning × school functioning	-0.000027	5063.2	6569.7
	Mapped EQ-5D	**0.82**	**0.89**

B.3.4.3 Health-related quality-of-life studies

Appendix H describes the conduct of systematic searches for relevant health-related quality-of-life data.

No HRQoL data suitable for inclusion in the economic model were identified by SLR.

B.3.4.4 Adverse reactions

The main adverse reactions associated with setmelanotide treatment comprise skin hyperpigmentation, injection site reactions and transient nausea and vomiting. None of these adverse reactions are expected to have a significant impact on HRQoL.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The model captured quality of life impact through five pathways: 1) BMI/BMI Z-score category, 2) hyperphagia severity, 3) disutility of obesity-related comorbidities, 4) disutility of non-obesity-related BBS symptoms, and 5) caregiver disutility. Total HRQoL values were calculated by applying hyperphagia-severity utility-multipliers to BMI/BMI Z-score utility values, applying a QALY multiplier for BBS symptoms, and then applying comorbidity and caregiver disutilities as absolute decrements. Daily injection was assumed to have a negligible impact on HRQoL.

Utility by BMI/BMI Z-score level

Baseline utility values were calculated for each treatment arm based on the distribution of patients across BMI Z-score categories; these are impacted by whether the patient remains on or discontinues setmelanotide treatment. As no reliable HRQoL data for the BBS population were identified by literature search or in clinical trials, utility values were obtained from other literature on HRQoL impact within the general obese population. Paediatric BBS patient population utility values for two BMI Z-score categories were taken from a clinical study of a UK obese paediatric population that completed PedsQL. Mapping of these data from PedsQL to EQ-5D is described in Section B.3.4.2, with the resulting utility values by BMI Z-score category shown in Table 62.

Table 62 Paediatric BBS patient utility values by BMI Z-score (Riazi 2010)

BMI Z-score	Utility value for age 6 to 17 years
0.0 to <1.0	0.89
1.0 to <2.0	0.87
2.0 to <2.5	0.86
2.5 to <3.0	0.85
3.0 to <3.5	0.83
3.5 to <4.0	0.82
≥4.0	0.81

HRQoL values by BMI score for BBS patients aged ≥18 years were based on Medical Expenditure Panel Survey data from published literature; these values

varied with age (Table 63), thereby addressing the tenet that quality of life generally decreases as patients age.

Table 63 Adult BBS patient utility values by BMI (Alsumali 2018)

BMI	Age (years)					
	18 to 30	31 to 40	41 to 50	51 to 60	61 to 70	>70
20 to <25 kg/m^2	0.91	0.89	0.86	0.83	0.81	0.79
25 to <30 kg/m^2	0.91	0.89	0.86	0.83	0.81	0.79
30 to <35 kg/m^2	0.89	0.86	0.82	0.80	0.79	0.76
35 to <40 kg/m^2	0.88	0.83	0.79	0.77	0.76	0.74
40 to <45 kg/m^2	0.84	0.82	0.75	0.73	0.71	0.69
45 to <50 kg/m^2	0.84	0.82	0.75	0.73	0.71	0.69
≥50 kg/m^2	0.80	0.77	0.70	0.69	0.66	0.66

Hyperphagia severity

Utility multipliers for mild, moderate, and severe hyperphagia were obtained from a vignette study described in Appendix O, and were applied to each BMI/BMI Z-score utility value (data on file). Utility multipliers were: 0.909 for mild hyperphagia; 0.702 for moderate hyperphagia; and [redacted] for severe hyperphagia.

Comorbidity disutility

The impact of comorbidities on quality of life were applied as comorbidity-specific disutilities to utility values using an additive approach, which aligned with published methodologies (Ara 2010). Disutility values were identified using multiple approaches, including an SLR for HRQoL data in the general obese population and targeted searches to fill data gaps. Data for sleep apnoea, osteoarthritis, and T2DM were obtained from the results of a multiple linear regression model of HRQoL based on Health Survey for England data reported by Søltoft 2009.

The cardiovascular event disutility was derived using individual event disutilities including myocardial infarction, angina, stroke, and transient ischaemic attack. A composite cardiovascular event disutility was calculated by weighting individual-event disutilities by the frequency of each when a cardiovascular event occurred. Table 64. Both sources were also used to populate comorbidity disutilities in the relevant NICE evidence submission for liraglutide in the management of overweight and obesity (NICE 2020a) and the recent HST submission for setmelanotide for

treatment of obesity caused by LEPR/POMC deficiency (NICE 2022). Cardiovascular event disutilities Table 64 using the frequency-weighting for each event from Table ***57***, and the final average disutility for each comorbidity is presented Table 65.

Table 64 Cardiovascular event disutilities

Event	Disutility	Source
Myocardial infarction	0.037	Sullivan 2011 Catalogue of EQ-5D scores for the UK, supplementary material in web Table 5
Angina	0.063	
Stroke	0.117	
Transient ischaemic attack	0.033	

Table 65 Comorbidity disutilities

Comorbidity	Disutility	Source
Sleep apnoea	0.034	Søltoft 2009 The association of BMI and HRQoL in the general population: Data from the 2003 Health Survey of England
Osteoarthritis	0.187	
T2DMM	0.043	
NASH	0.000	NICE 2016 No added disutility assumed based on the NAFLD Guideline Development Group suggestion to consider utility for NAFLD as similar to that for obese patients
Cardiovascular events	0.066	Sullivan 2011 Catalogue of EQ-5D scores for the UK, supplementary data. Weighted based on the proportion of cardiovascular events in Table 57

The impact of comorbidities on quality of life was shown to increase with obesity severity; each comorbidity disutility was disaggregated along a log-linear distribution using the same BMI Z-score and standard deviations as used to estimate mortality by BMI/BMI Z-score. This resulted in individual disutilities by BMI/BMI Z-score category for each comorbidity as shown in Table 66.

Table 66 Comorbidity disutility by BMI Z-score category

BMI Z-score	Sleep apnoea	Osteoarthritis	NASH	T2DMM	Cardiovascular events
0.0 to 1.0	0.000	0.000	0.000	0.000	0.000
1.0 to 2.0	0.022	0.062	0.000	0.025	0.033
2.0 to 2.5	0.026	0.098	0.000	0.032	0.044
2.5 to 3.0	0.032	0.154	0.000	0.040	0.060
3.0 to 3.5	0.039	0.244	0.000	0.050	0.081
3.5 to 4.0	0.047	0.385	0.000	0.064	0.109
>4.0	0.057	0.607	0.000	0.080	0.146

BBS symptoms

The quality-of-life impact of non-obesity-related BBS symptoms such as blindness and cognitive impairment were accounted for by using an additional QALY multiplier that was estimated at 0.8.

Caregiver burden

Caregiver burden was also accounted for in quality-of-life estimates, as has been accepted in previous NICE submissions (NICE 2015, NICE 2021). The annual disutility attributable to caregivers was implemented as in the NICE submission for metreleptin for treatment of lipodystrophy (NICE 2021), based on evidence from Janssen 2019 and UK general population norms. The lipodystrophy population was selected because it has similar attributes to the BBS population, as it can lead to obesity and severe comorbidities with the primary treatment being diet and lifestyle modification; as with BBS, there is a significant impact on carer utility with impairment in daily activities and quality of life. This utility decrement was applied assuming an average of 1.5 caregivers per paediatric patient and 1 caregiver per adult patient, with a disutility of 0.0986.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Error! Reference source not found. describes how relevant cost and healthcare resource data were identified.

B.3.5.1 Intervention and comparator costs and resource use

The unit cost for setmelanotide is Commercial in confidence data removed, which represents a Commercial in confidence data removed discount on the reference NHS list price. Annual costs for setmelanotide were calculated using the average patient dose from clinical trial for Day 1 and during titration, combined with the expected post-titration dose for the real-world population. The starting dose, dose during titration, and post-titration dose were used to calculate average Year 1 costs for both paediatric and adult patients with BBS.

- With an average starting dose for paediatric patients with BBS of Commercial in confidence data removed on Day 1, a 2-week titration-period dose of Commercial in confidence data removed, and a predicted Commercial in confidence data removed post-titration dose, the average Year 1 setmelanotide dose was Commercial in confidence data removed a day. The average daily setmelanotide dose for Years 2 and onward was assumed to be equivalent to the Commercial in confidence data removed mg post-titration dose.
- With an average starting dose for adult patients with BBS of Commercial in confidence data removed on Day 1, a 2-week titration-period dose of Commercial in confidence data removed, and a predicted Commercial in confidence data removed post-titration dose, the average Year 1 setmelanotide dose was Commercial in confidence data removed a day. The average daily setmelanotide dose for Years 2 and onward was assumed to be equivalent to the Commercial in confidence data removed dose post-titration dose.

It was assumed that there would be no wastage costs, as remaining medication can be used for additional doses. Setmelanotide administration costs were assumed to be negligible, as patients are expected to be able to self-administer their dose daily with the help of their caregiver.

BSC administration costs are assumed to be accounted for in general obesity-management costs, with no additional resource use as diet and exercise instruction is expected to occur during regular physician visits and be encompassed in monitoring costs. Monitoring costs for setmelanotide and BSC comprise complete blood count, liver function tests, comprehensive metabolic panel, and regular physician visits; test/visit frequency was assumed to be the same for BBS as those

used in previous POMC/LEPR submission (HST21). The annual frequency and units costs of monitoring BBS patients are presented in Table 67.

Table 67 Monitoring and costs for BBS patients receiving setmelanotide and/or best supportive care

Resource	Unit cost	Annual visits		Source
		Setmelanotide + BSC	BSC	
Complete blood count	£2.79	1	1	National schedule of NHS costs, 2018 to 2019 (Curtis 2019) Unit costs of health and social care 2020
Liver function test	£8.79	1	1	
Comprehensive metabolic panel	£15.38	1	1	
Physician visit	£39.23	1	4	Based on a general practitioner visit (per patient contact of 9.22 minutes)

The costs associated with setmelanotide with BSC and BSC alone are summarised in Table 68.

Table 68 Cost of setmelanotide treatment and best supportive care for patients with BBS

Items	Setmelanotide (confidence interval)	BSC (confidence interval)
Technology cost	Commercial in confidence data removed	NA
Paediatric cost year 1	Commercial in confidence data removed	£0.00
Paediatric cost years 2+	Commercial in confidence data removed	£0.00
Adult cost year 1	Commercial in confidence data removed	£0.00
Adult cost years 2+	Commercial in confidence data removed	£0.00
Monitoring cost	Commercial in confidence data removed	£183.88 (147.84 to 219.92)

B.3.5.2 Health-state unit costs and resource use

Costs for each BMI/BMI Z-score category were informed by a published cost-effectiveness analysis of obesity interventions based on UK Biobank data that included both primary and secondary healthcare costs (Harrison 2021). Primary costs included prescribed drugs and general practitioner visits; secondary costs

included hospital costs calculated from Healthcare Resource groups from linked hospital-episode data excluding emergency care or outpatient appointments. Results from the reported age interaction Mendelian randomisation and multivariable adjusted analysis were used to account for the expected variation in healthcare costs due to age. These costs reflect general healthcare utilisation by obese patients and do not inform on use for non-obesity related BBS comorbidities that are likely to be present in the modelled population. Cost inputs for each health state are shown in Table 69 for paediatric and Table 70 for adult patients.

Table 69 Cost input by BMI Z-score category in adult paediatric patients

BMI Z-score	Age <18 years
0.0 to <1.0	£0
1.0 to <2.0	£997
2.0 to <2.5	£1,336
2.5 to <3.0	£1,688
3.0 to <3.5	£2,052
3.5 to <4.0	£2,428
≥4.0	£2,818

Table 70 Cost input by BMI category and age in adult patients

	Age (years)					
BMI	**18 to 30**	**31 to 40**	**41 to 50**	**51 to 60**	**61 to 70**	**>70**
20 to <25 kg/m^2	£0	£0	£0	£0	£0	£0
25 to <30 kg/m^2	£997	£1,445	£1,852	£2,260	£2,667	£3,075
30 to <35 kg/m^2	£1,336	£1,931	£2,472	£3,013	£3,554	£4,095
35 to <40 kg/m^2	£1,688	£2,435	£3,114	£3,793	£4,472	£5,151
40 to <45 kg/m^2	£2,052	£2,956	£3,778	£4,600	£5,422	£6,244
45 to <50 kg/m^2	£2,428	£3,495	£4,465	£5,435	£6,405	£7,375
≥50 kg/m^2	£2,818	£4,054	£5,177	£6,301	£7,424	£8,547

Comorbidities costs were identified by targeted literature search. Sources for sleep apnoea, osteoarthritis, T2DM, and cardiovascular events used the previous NICE submission for setmelanotide in LEPR/POMC patients (NICE 2022), with no updated values identified. The annual costs for NASH were sourced from a 2018 UK cost of illness study (Morgan 2021); direct healthcare costs for the lower prevalence NASH population were used.

The annual cost of managing cardiovascular events was based on a weighted average of long-term costs for each event (Danese 2016), weighted by proportion of all cardiovascular events (D'Agostino 2008, D'Agostino 2016) to create a composite cardiovascular event endpoint; the proportion for each cardiovascular event are presented in Table 57 and the costs for each event are shown in Table 71. Average annual costs associated with each comorbidity are presented in Table 72.

Table 71 Costs for cardiovascular events (Danese 2016)

Type of cardiovascular event	Cost
Myocardial infarction	£2,472.28
Angina	£2,179.64
Stroke	£2,545.10
Transient ischaemic attack	£2,447.92

Table 72 Average annual comorbidity costs

Comorbidity	Value	Source
Sleep apnoea	£1,614.71	McMillan (2015)
Osteoarthritis	£1,013.72	The economic costs of arthritis for the UK economy
NASH	£963.23	Morgan (2018)
T2DMM	£3,263.67	Currie (2007)
Cardiovascular events	£2,751.41	Danese (2016), D'Agostino 2000, D'Agostino (2008)

The cost of comorbidities would be expected to increase by BMI/BMI Z-score category, as a result of greater severity at higher obesity levels. Thus, a linear distribution was applied to the average cost of each comorbidity by BMI Z-score category using the same average BMI Z-score and standard deviation distributions previously used for comorbidity disutility and the SMR for early-onset obesity. This resulted in increasing comorbidity cost by BMI Z-score category as shown in Table ***73***.

Table 73 Annual comorbidity costs by BMI Z-score category

BMI Z-score	Sleep apnoea	Osteoarthritis	NASH	T2DMM	Cardiovascular events
0.0 to <1.0	£514.27	£322.86	£125.63	£1,039.44	£876.29
1.0 to <2.0	£1,028.53	£645.72	£251.27	£2,078.88	£1,752.58
2.0 to <2.5	£1,285.66	£807.14	£314.08	£2,598.59	£2,190.73
2.5 to <3.0	£1,542.80	£968.57	£376.90	£3,118.31	£2,628.87
3.0 to <3.5	£1,799.93	£1,130.00	£439.72	£3,638.03	£3,067.02
3.5 to <4.0	£2,057.06	£1,291.43	£502.53	£4,157.75	£3,505.16
≥4.0	£2,314.20	£1,452.86	£565.35	£4,677.47	£3,943.31

Adverse reaction unit costs and resource use

No adverse reactions were included in the model (Section B.2.10). This assumption is consistent with that of the analysis for setmelanotide in the LEPR/POMC deficiency population (NICE 2022).

Miscellaneous unit costs and resource use

No additional costs were incorporated in the cost-effectiveness analysis.

B.3.6 Uncertainty

By their nature, rare diseases present recruitment challenges in clinical trials. The pivotal clinical trial recruited 32 patients into the pivotal cohort and, as a result, some analyses in the economic model rely on small patient numbers (e.g. BMI category shift data is based on 7 adults; BMI Z-score category shift data is based on 12 paediatric patients).

Hyperphagia is an emerging therapy area and validated methods of measuring hyperphagia in BBS patients do not exist. Hyperphagia was not measured in the trial and it was not, therefore, possible to collect direct evidence of the impact of setmelanotide treatment on hyperphagia. As a result, assumptions were made based on the link between hyperphagia and weight; specifically that hyperphagia, as the underlying cause of obesity, must be reduced significantly in order for patients to experience the level of weight loss seen in clinical trials. It was therefore assumed that all patients entered the trial with severe hyperphagia and that all patients who responded to setmelanotide in terms of experiencing a clinically meaningful reduction in weight, did so because setmelanotide reduced their hyperphagia symptoms to mild.

While EQ-5D is a valid instrument for calculating HRQoL in patients with obesity, it is unlikely to be sensitive to the severe insatiable hunger (hyperphagia) that patients with BBS and obesity experience. Previous HRQoL studies reflect the general obese population and do not characterise the impact of hyperphagia, independent of obesity, on HRQoL.

There is increasing recognition of the limitations of EQ-5D for capturing health changes in certain populations, including those with mental health and sensory deprivation (visual or hearing impairment). This was also acknowledged by NICE in its Centre for Health Technology Evaluation Methods Review (NICE 2020b). These limitations include: EQ-5D not reflecting quality of life for these conditions; and that changes in health are seen to have a small impact on quality of life when assessed using EQ-5D. In the case of BBS patients, hyperphagia is a serious condition that has substantial effect on HRQoL; however, none of the EQ-5D dimensions captures hyperphagia. Hyperphagia may be considered a sensory deprivation condition, as it is characterised by impaired satiety whereby patients constantly feel hungry, even after eating; EQ-5D has been shown to not be sensitive to sensory deprivation conditions (Perneger 2011).

In addition, certain disease populations may adapt to their condition (Yang 2013, Longworth 2014, Brazier 2019). BBS is a genetic disease and hyperphagia is experienced from birth. Given the early manifestation of hyperphagia in patients with BBS, affected adult patients may be unable to fully recognise the severity of their hunger as it is their ‘normal’ state to which they have adapted to from an early age. Results from exit interviews conducted with patients and caregivers of patients who participated in setmelanotide clinical trials for treatment of obesity due to BBS support this tenet:

“After we started this setmelanotide trial, she told me for the first time that she had no idea what it was not to be hungry… So before the trial, I guess, according to her she had never experienced not being hungry before.” Caregiver of a patient with BBS

This is further indicated by pain/discomfort dimension EQ-5D scores reported at baseline for which the mean was [redacted] on a scale of 1 to 5, indicating that the average patient fell somewhere between having

[redacted]. Were this dimension effectively capturing the impact of hyperphagia, a higher score would be anticipated as the average daily hunger questionnaire score was 6.45 at baseline (the upper end of the moderate hunger category).

Further, individuals with hyperphagia due to BBS may have developed coping strategies due to the early onset of symptoms, which could influence the ability of quality of life measures to detect health changes. This may be particularly true for the five dimensions assessed by EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), as has been seen with other sensory conditions (Payakachat 2015).

Accordingly, EQ-5D may not be sensitive enough detect the magnitude of quality of life impact in patients with hyperphagia and obesity due to BBS; this is likely to mean that the quality of life benefits of interventions to address hyperphagia will be similarly underestimated.

NICE states that “In some circumstances the EQ-5D may not be the most appropriate. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence on the lack of content validity for the EQ-5D should be provided, demonstrating that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity and responsiveness in a particular patient population. This evidence should be derived from a synthesis of peer-reviewed literature” (NICE 2013). No studies have been conducted that test whether EQ-5D is responsive to hyperphagia, since genetic hyperphagia conditions are rare. The most recent proposal for updates to NICE HTA guidelines regarding health-related quality of life states that “For rare diseases, there may not be sufficient published literature to provide evidence that the EQ-5D does not perform well. However, although there may not be evidence available to show that the EQ-5D performs poorly on psychometric measures for a rare disease, a lack of content validity could be supported, by providing evidence that the EQ-5D lacks specific dimensions of health that are important to patients.” (NICE 2020b).

Given the guidance and the evidence presented, we concluded that the EQ-5D is not appropriate for measuring HRQoL in patients with BBS with hyperphagia and obesity. Therefore, utility data to inform the model were obtained from published

literature on cohorts of general obese patients that were modified using utility multipliers and disutilities to account for the impact of BBS.

B.3.7 Managed access proposal

A managed access proposal is not being submitted.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

Variables applied to the economic model are summarised in Table 74.

Table 74 Summary of variables applied in the economic model

Variable	Value	Distribution	Alpha	Beta	Section
Demographic characteristics					
Age, paediatric	6	NA	NA	NA	Patient population, Section B.3.2.1
% Female, paediatric	50%	NA	NA	NA	Table 12
Baseline BMI Z-score distribution					
0.0 to <1.0	0%	Dirichlet	0.00	1.00	Table 13
1.0 to <2.0	6%	Dirichlet	1.00	1.00	
2.0 to <2.5	6%	Dirichlet	1.00	1.00	
2.5 to <3.0	13%	Dirichlet	2.00	1.00	
3.0 to <3.5	19%	Dirichlet	3.00	1.00	
3.5 to <4.0	19%	Dirichlet	3.00	1.00	
≥4.0	38%	Dirichlet	6.00	1.00	
Baseline hyperphagia distribution					
Mild	0%	NA	NA	NA	Patient population, Section B.3.2.1
Moderate	0%	NA	NA	NA	
Severe	100%	NA	NA	NA	
Setmelanotide efficacy					
Response rate, paediatric	86%	Beta	18.00	3.00	Treatment effect, Section B.3.3.2
Decrease in BMI Z-score, paediatric	2	NA	NA	NA	
Treatment discontinuation	1%	Beta	98.99	9800.01	
Setmelanotide treatment effect on hyperphagia					
Severe to mild	100%	NA	NA	NA	Treatment effect, Section B.3.3.2
Severe to moderate	0%	NA	NA	NA	
Moderate to mild	100%	NA	NA	NA	
SMR for early onset obesity[a]					

Variable	Value	Distribution	Alpha	Beta	Section
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	1.00	NA	NA	NA	Mortality, Section B.3.3.4
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	1.99	Lognormal	0.69	0.07	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	2.36	Lognormal	0.86	0.09	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	2.80	Lognormal	1.03	0.10	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	3.33	Lognormal	1.20	0.12	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	3.96	Lognormal	1.38	0.14	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	4.70	Lognormal	1.55	0.15	
SMR by BMI/BMI Z-score (general obesity)					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	1.00	NA	NA	NA	Mortality, Section B.3.3.4
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	1.21	Lognormal	0.19	0.10	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	1.46	Lognormal	0.38	0.10	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	1.77	Lognormal	0.57	0.10	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	2.14	Lognormal	0.76	0.10	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	2.59	Lognormal	0.95	0.10	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	3.14	Lognormal	1.14	0.10	
Utility by BMI Z-score					
0.0 to <1.0	0.89	Beta	10.41	1.33	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
1.0 to <2.0	0.87	Beta	11.74	1.69	
2.0 to <2.5	0.86	Beta	13.07	2.11	
2.5 to <3.0	0.85	Beta	14.40	2.59	
3.0 to <3.5	0.83	Beta	15.72	3.12	
3.5 to <4.0	0.82	Beta	17.05	3.71	
≥4.0	0.81	Beta	18.38	4.37	
Utility by BMI: age 18 to 30 years					
20 to <25 kg/m^2	0.91	Beta	8.09	0.80	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.91	Beta	8.09	0.80	
30 to <35 kg/m^2	0.89	Beta	10.11	1.25	
35 to <40 kg/m^2	0.88	Beta	11.12	1.52	
40 to <45 kg/m^2	0.84	Beta	15.16	2.89	
45 to <50 kg/m^2	0.84	Beta	15.16	2.89	
≥50 kg/m^2	0.80	Beta	19.20	4.80	
Utility by BMI: age 31 to 40 years					

Variable	Value	Distribution	Alpha	Beta	Section
20 to <25 kg/m^2	0.89	Beta	10.11	1.25	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.89	Beta	10.11	1.25	
30 to <35 kg/m^2	0.86	Beta	13.14	2.14	
35 to <40 kg/m^2	0.83	Beta	16.17	3.31	
40 to <45 kg/m^2	0.82	Beta	17.18	3.77	
45 to <50 kg/m^2	0.82	Beta	17.18	3.77	
≥50 kg/m^2	0.77	Beta	22.23	6.64	
Utility by BMI: age 41 to 50 years					
20 to <25 kg/m^2	0.86	Beta	13.14	2.14	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.86	Beta	13.14	2.14	
30 to <35 kg/m^2	0.82	Beta	17.18	3.77	
35 to <40 kg/m^2	0.79	Beta	20.21	5.37	
40 to <45 kg/m^2	0.75	Beta	24.25	8.08	
45 to <50 kg/m^2	0.75	Beta	24.25	8.08	
≥50 kg/m^2	0.70	Beta	29.30	12.56	
Utility by BMI: age 51 to 60 years					
20 to <25 kg/m^2	0.83	Beta	16.17	3.31	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.83	Beta	16.17	3.31	
30 to <35 kg/m^2	0.80	Beta	19.20	4.80	
35 to <40 kg/m^2	0.77	Beta	22.23	6.64	
40 to <45 kg/m^2	0.73	Beta	26.27	9.72	
45 to <50 kg/m^2	0.73	Beta	26.27	9.72	
≥50 kg/m^2	0.69	Beta	30.31	13.62	
Utility by BMI: age 61 to 70 years					
20 to <25 kg/m^2	0.81	Beta	18.19	4.27	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.81	Beta	18.19	4.27	
30 to <35 kg/m^2	0.79	Beta	20.21	5.37	
35 to <40 kg/m^2	0.76	Beta	23.24	7.34	
40 to <45 kg/m^2	0.71	Beta	28.29	11.56	
45 to <50 kg/m^2	0.71	Beta	28.29	11.56	
≥50 kg/m^2	0.66	Beta	33.34	17.18	
Utility by BMI: age >70 years					
20 to <25 kg/m^2	0.79	Beta	20.21	5.37	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
25 to <30 kg/m^2	0.79	Beta	20.21	5.37	
30 to <35 kg/m^2	0.76	Beta	23.24	7.34	
35 to <40 kg/m^2	0.74	Beta	25.26	8.88	
40 to <45 kg/m^2	0.69	Beta	30.31	13.62	
45 to <50 kg/m^2	0.69	Beta	30.31	13.62	
≥50 kg/m^2	0.66	Beta	33.34	17.18	
Hyperphagia utility multiplier					
Mild	0.91	Beta	1522.91	152.46	HRQoL data used in the cost-effectiveness
Moderate	0.70	Beta	345.49	146.66	

Variable	Value	Distribution	Alpha	Beta	Section
Severe	[redacted]	Beta	55.67	90.84	analysis, Section B.3.4.5
BBS utility decrement multiplier	0.80	Gamma	100.00	0.01	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
Caregiver burden					
Number of caregivers, paediatric	1.50	Gamma	100.00	0.02	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
Utility decrement, paediatric	-0.10	Beta	90.04	823.16	
Number of caregivers adult	1.00	Gamma	100.00	0.01	
Utility decrement adult	-0.10	Beta	90.04	823.16	
Sleep apnoea disutilities[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	0.000	Normal	NA	NA	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	0.022	Normal	0.02	0.00	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	0.026	Normal	0.03	0.00	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	0.032	Normal	0.03	0.00	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	0.039	Normal	0.04	0.00	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	0.047	Normal	0.05	0.00	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	0.057	Normal	0.06	0.01	
Osteoarthritis disutilities[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	0.000	Normal	NA	NA	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	0.062	Normal	0.06	0.01	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	0.098	Normal	0.10	0.01	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	0.154	Normal	0.15	0.02	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	0.244	Normal	0.24	0.02	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	0.385	Normal	0.38	0.04	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	0.607	Normal	0.61	0.06	
NASH disutilities[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	0.000	NA	NA	NA	HRQoL data used in the cost-

Variable	Value	Distribution	Alpha	Beta	Section
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	0.000	NA	NA	NA	effectiveness analysis, Section B.3.4.5
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	0.000	NA	NA	NA	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	0.000	NA	NA	NA	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	0.000	NA	NA	NA	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	0.000	NA	NA	NA	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	0.000	NA	NA	NA	
T2DMM disutilities[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	0.000	Normal	NA	NA	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	0.025	Normal	0.03	0.00	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	0.032	Normal	0.03	0.00	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	0.040	Normal	0.04	0.00	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	0.050	Normal	0.05	0.01	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	0.064	Normal	0.06	0.01	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	0.080	Normal	0.08	0.01	
Cardiovascular event disutilities[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	0.000	Normal	NA	NA	HRQoL data used in the cost-effectiveness analysis, Section B.3.4.5
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	0.033	Normal	0.03	0.00	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	0.044	Normal	0.04	0.00	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	0.060	Normal	0.06	0.01	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	0.081	Normal	0.08	0.01	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	0.109	Normal	0.11	0.01	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	0.146	Normal	0.15	0.01	
BMI Z-score related healthcare costs (paediatric)					
0.0 to <1.0	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
1.0 to <2.0	£997	Gamma	100.00	9.97	
2.0 to <2.5	£1,336	Gamma	100.00	13.36	
2.5 to <3.0	£1,688	Gamma	100.00	16.88	

Variable	Value	Distribution	Alpha	Beta	Section
3.0 to <3.5	£2,052	Gamma	100.00	20.52	
3.5 to <4.0	£2,428	Gamma	100.00	24.28	
≥4.0	£2,818	Gamma	100.00	28.18	
BMI-related healthcare costs: age 18 to 30 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£997	Gamma	100.00	9.97	
30 to <35 kg/m^2	£1,336	Gamma	100.00	13.36	
35 to <40 kg/m^2	£1,688	Gamma	100.00	16.88	
40 to <45 kg/m^2	£2,052	Gamma	100.00	20.52	
45 to <50 kg/m^2	£2,428	Gamma	100.00	24.28	
≥50 kg/m^2	£2,818	Gamma	100.00	28.18	
BMI-related healthcare costs: age 31 to 40 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£1,445	Gamma	100.00	14.45	
30 to <35 kg/m^2	£1,931	Gamma	100.00	19.31	
35 to <40 kg/m^2	£2,435	Gamma	100.00	24.35	
40 to <45 kg/m^2	£2,956	Gamma	100.00	29.56	
45 to <50 kg/m^2	£3,495	Gamma	100.00	34.95	
≥50 kg/m^2	£4,054	Gamma	100.00	40.54	
BMI-related healthcare costs: age 41 to 50 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£1,852	Gamma	100.00	18.52	
30 to <35 kg/m^2	£2,472	Gamma	100.00	24.72	
35 to <40 kg/m^2	£3,114	Gamma	100.00	31.14	
40 to <45 kg/m^2	£3,778	Gamma	100.00	37.78	
45 to <50 kg/m^2	£4,465	Gamma	100.00	44.65	
≥50 kg/m^2	£5,177	Gamma	100.00	51.77	
BMI-related healthcare costs: age 51 to 60 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£2,260	Gamma	100.00	22.60	
30 to <35 kg/m^2	£3,013	Gamma	100.00	30.13	
35 to <40 kg/m^2	£3,793	Gamma	100.00	37.93	
40 to <45 kg/m^2	£4,600	Gamma	100.00	46.00	
45 to <50 kg/m^2	£5,435	Gamma	100.00	54.35	
≥50 kg/m^2	£6,301	Gamma	100.00	63.01	
BMI-related healthcare costs: age 61 to 70 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£2,667	Gamma	100.00	26.67	
30 to <35 kg/m^2	£3,554	Gamma	100.00	35.54	
35 to <40 kg/m^2	£4,472	Gamma	100.00	44.72	
40 to <45 kg/m^2	£5,422	Gamma	100.00	54.22	
45 to <50 kg/m^2	£6,405	Gamma	100.00	64.05	

Variable	Value	Distribution	Alpha	Beta	Section
≥50 kg/m^2	£7,424	Gamma	100.00	74.24	
BMI-related healthcare costs: age >70 years					
20 to <25 kg/m^2	£0	NA	NA	NA	Health-state unit costs and resource use, Section B.3.5.2
25 to <30 kg/m^2	£3,075	Gamma	100.00	30.75	
30 to <35 kg/m^2	£4,095	Gamma	100.00	40.95	
35 to <40 kg/m^2	£5,151	Gamma	100.00	51.51	
40 to <45 kg/m^2	£6,244	Gamma	100.00	62.44	
45 to <50 kg/m^2	£7,375	Gamma	100.00	73.75	
≥50 kg/m^2	£8,547	Gamma	100.00	85.47	
Treatment costs: setmelanotide					
Paediatric year 1	Commercial in confidence data removed	Gamma	Commercial in confidence data removed	Commercial in confidence data removed	Intervention and comparator costs and resource use, Section B.3.5.1
Paediatric years 2+	Commercial in confidence data removed	Gamma	Commercial in confidence data removed	Commercial in confidence data removed	
Adult year 1	Commercial in confidence data removed	Gamma	Commercial in confidence data removed	Commercial in confidence data removed	
Adult years 2+	Commercial in confidence data removed	Gamma	Commercial in confidence data removed	Commercial in confidence data removed	
Unit Cost Discount	Commercial in confidence data removed	Gamma	Commercial in confidence data removed	Commercial in confidence data removed	
Annual treatment cost: BSC	£0	NA	NA	NA	Intervention and comparator costs and resource use, Section B.3.5.1
Monitoring costs					
Setmelanotide	£66.00	Gamma	100.00	0.66	Intervention and comparator costs and resource use, Section B.3.5.1
BSC	£183.88	Gamma	100.00	1.84	
Sleep apnoea costs[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£514.27	Normal	514.27	51.43	Health-state unit cost and resource use, Section B.3.5.2
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£1,028.53	Normal	1028.53	102.85	
BMI 30 to <35 kg/m^2	£1,285.66	Normal	1285.66	128.57	

Variable	Value	Distribution	Alpha	Beta	Section
BMI Z-score 2.0 to <2.5					
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	£1,542.80	Normal	1542.80	154.28	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£1,799.93	Normal	1799.93	179.99	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£2,057.06	Normal	2057.06	205.71	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£2,314.20	Normal	2314.20	231.42	
Osteoarthritis costs[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£322.86	Normal	322.86	32.29	Health-state unit cost and resource use, Section B.3.5.2
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£645.72	Normal	645.72	64.57	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	£807.14	Normal	807.14	80.71	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	£968.57	Normal	968.57	96.86	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£1,130.00	Normal	1130.00	113.00	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£1,291.43	Normal	1291.43	129.14	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£1,452.86	Normal	1452.86	145.29	
NASH costs[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£125.63	Normal	125.63	12.56	Health-state unit cost and resource use, Section B.3.5.2
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£251.27	Normal	251.27	25.13	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	£314.08	Normal	314.08	31.41	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	£376.90	Normal	376.90	37.69	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£439.72	Normal	439.72	43.97	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£502.53	Normal	502.53	50.25	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£565.35	Normal	565.35	56.53	
T2DM costs[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£1,039.44	Normal	1039.44	103.94	Health-state unit cost and resource use, Section B.3.5.2
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£2,078.88	Normal	2078.88	207.89	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	£2,598.59	Normal	2598.59	259.86	
BMI 35 to <40 kg/m^2	£3,118.31	Normal	3118.31	311.83	

Variable	Value	Distribution	Alpha	Beta	Section
BMI Z-score 2.5 to <3.0					
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£3,638.03	Normal	3638.03	363.80	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£4,157.75	Normal	4157.75	415.78	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£4,677.47		4677.47	467.75	
Cardiovascular event costs[a]					
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£876.29	Normal	876.29	87.63	Health-state unit cost and resource use, Section B.3.5.2
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£1,752.58	Normal	1752.58	175.26	
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	£2,190.73	Normal	2190.73	219.07	
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	£2,628.87	Normal	2628.87	262.89	
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£3,067.02	Normal	3067.02	306.70	
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£3,505.16	Normal	3505.16	350.52	
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£3,943.31	Normal	3943.31	394.33	

[a] Perfect correlation across BMI Z-scores is assumed, as they are calibrated to the uncertainty in the underlying parameter (the average BMI value from Lindberg 2020).

B.3.8.2 Assumptions

Assumptions used in the economic model and a justification for each are presented in Table 75.

Table 75 Assumptions used in the economic model

Assumption	Justification
The risk of mortality in BBS patients is greater than that for the general obese population. An SMR for early-onset obesity related impact on mortality probability was applied to each BMI/BMI Z-score category.	This reflects the increased mortality risk for the BBS population incurred due to the early age at which they become obese.
There is an increased risk mortality for BBS patients as compared with the general obese population. An SMR of <1 was applied to setmelanotide responders to counteract BBS-related mortality.	There is significant benefit in treating early-onset obesity as early as possible, to prevent the development of comorbidities such as cardiovascular disease, dyslipidaemia, insulin resistance and T2DM, and NAFLD (Hampl 2023) all of which negatively affect life expectancy
The baseline hyperphagia distribution was assumed to be 100% severe hyperphagia.	Hyperphagia is the driving force behind the onset of obesity in BBS patients. Fifteen of 16 adult patients in trials had a BMI of

Assumption	Justification
	≥35 kg/m^2 and 12 of 16 paediatric patients had a BMI Z-score of ≥3; these are representative of patients with severe obesity. It was assumed that a high frequency of severe obesity was the result of severe hyperphagia.
Paediatric and adult populations were modelled similarly, with paediatric states defined using BMI Z-score and adult states using BMI score. Once patients in the paediatric cohort became adults (at age 18 years), their BMI Z-score state was mapped to an aligned BMI score state.	BMI Z-score is a more commonly accepted standard for characterising obesity in paediatric patients (Cole 1995).
BMI/BMI Z-score was assumed to be stable after responding to treatment and thus BMI/BMI Z-score level remained equivalent to the 52-week endpoint unless a patient discontinued treatment.	Pomeroy 2021 showed that BMI Z-score for BBS patients peaked at 2 to 5 years of age and subsequently decreased or stabilised.
Setmelanotide was assumed to have no administration cost.	Patients self-administer setmelanotide. Training in setmelanotide administration will be provided to patients and carers, as part of a patient support program.
Setmelanotide non-responders were assumed to discontinue treatment after 14 weeks.	Hunger levels fall rapidly on initiation of setmelanotide treatment. It was, therefore, assumed that clinicians can accurately identify patient response at 14 weeks based on changes in hyperphagia and other clinical parameters. At this timepoint, non-responders would be discontinued.
Under standard of care, patients with BBS with obesity aged 6 to 18 years maintained the same BMI Z-score as they aged. Patients with BBS with obesity aged >18 years maintained the same BMI over time under standard of care (i.e., they maintained approximately the same weight).	Based on clinical expert opinion.
Distribution amongst BMI/BMI Z-score categories remained constant in each year of the model, aside from treatment impact after year 1 or discontinuation effects.	Based on clinical expert opinion.
Setmelanotide non-responders discontinued treatment at the 14-week endpoint and were assumed to experience no treatment effect during Year 1 of the model. Thus, these patients did not change from their baseline BMI/BMI Z-score category. Patients who discontinued after 52 weeks were assumed to lose treatment effect at time of discontinuation, and return	A lack of tapering of treatment effects was a conservative assumption, made due to a lack of data regarding ongoing treatment effect for discontinued patients.

Assumption	Justification
to their original BMI/BMI Z-score category.	
Comorbidity prevalence inputs were modelled based on the literature for morbidly obese patients eligible for weight-loss surgery.	No data were identified that detailed comorbidities in the BBS population. Comorbidity prevalence for morbidly obese patients eligible for weight-loss surgery were used as a proxy.
Comorbidity prevalence was assumed to vary with BMI/BMI Z-score.	No evidence was found in the SLR to stratify the prevalence of modelled comorbidities by both BMI and age.
Cancer was not considered as a comorbidity in the model and cardiovascular disease and T2DM were assumed to only occur in adults.	Cardiovascular disease and T2DM are not key risk factors for paediatric patients and patients are expected to die before they develop cancer based on clinical expert opinion.
Utility by hyperphagia was applied multiplicatively to BMI/BMI Z-score and age-specific utility values. Hyperphagia utility multipliers were informed by the vignette study (Appendix O).	The multiplicative approach is a recommended method to represent the utility effects of multiple concurrent clinical events (Brazier 2019).
Hyperphagia severity was modelled separately from BMI/BMI Z-score.	Patient-level data to inform health states, detailing the combined clinical and economic outcomes by BMI/BMI Z-score category and hyperphagia level were not available. Due to the all-consuming nature of hyperphagia it is assumed to have a separate impact on quality of life, that is independent of the impact of obesity.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

Base-case results for the incremental cost-effectiveness analysis for setmelanotide in paediatric patients with BBS are presented in Table 76.

Table 76 Base-case the cost-effectiveness analysis results for setmelanotide in paediatric patients with BBS

	Setmelanotide	Best supportive care
Total cost	Commercial in confidence data removed	£111,936
Total life-years gained	Commercial in confidence data removed	24.11
Total quality-adjusted life years	Commercial in confidence data removed	0.89
Total undiscounted quality-adjusted life years	Commercial in confidence data removed	2.83
Incremental costs	Commercial in confidence data removed	
Incremental life years gained	Commercial in confidence data removed	
Incremental quality-adjusted life years	Commercial in confidence data removed	
Incremental undiscounted quality-adjusted life years	Commercial in confidence data removed	
Incremental cost-effectiveness ratio	£191,759/QALY	

Appendix J presents disaggregated results of the base-case incremental cost-effectiveness analysis.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to account for potential variation and uncertainty in model inputs. The appropriate distribution for each variable was chosen based on expected and plausible values for each, as detailed in Table 74. A beta distribution was assumed for independent probability variables such as treatment response rate. Baseline distribution among BMI Z-score categories were varied along a Dirichlet distribution. A beta distribution was also assumed for utility and disutility values. All cost inputs were varied on a gamma distribution, as was the number of caregivers. SMR variables were assumed to follow a log-normal distribution. SMRs for BBS patients by BMI were varied along a log-normal distribution, while comorbidity costs and disutilities were varied along a normal distribution and assuming perfect correlation across BMI Z-scores as all were calibrated to the uncertainty in the underlying parameter (the average BMI value from Lindberg 2020). Standard errors were calculated using source data where

available, and a 10% standard error was assumed for variables where cohort size was unavailable. The probabilistic sensitivity analysis (Figure 13) consisted of 1000 simulation runs to allow for stable results.

Figure 13 Probabilistic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide in paediatric patients with BBS

Commercial in confidence data removed

A cost-effectiveness acceptability curve was generated which detailed the probability of cost-effectiveness for each intervention at 201 willingness to pay thresholds that varied from £0 to £1,000,000 at £5,000 intervals. The cost-effectiveness acceptability frontier curve shows that at a threshold of £195,000, setmelanotide becomes more likely to be cost-effective than BSC (Figure 14).

Figure 14 Setmelanotide cost-effectiveness acceptability curve for use in paediatric patients with BBS

Commercial in confidence data removed

B.3.10.2 Deterministic sensitivity analysis

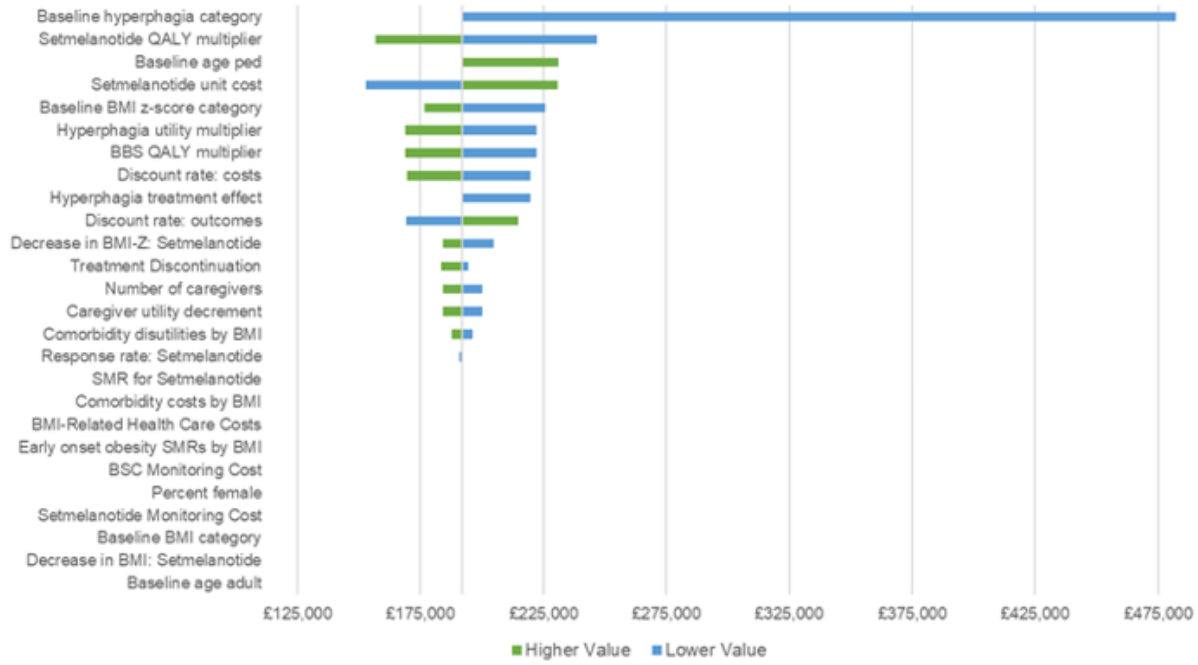
One-way deterministic sensitivity analysis was conducted for all driving model variables. Significant uncertainty exists in model inputs due to the small population sizes in clinical trials of setmelanotide treatment in patients with BBS, so modelling sensitivity to baseline variables was essential.

Model inputs were varied by 20% in either direction when logical. When this variation did not align with variable constraints, an absolute change was considered for the input. Some variables (such as hyperphagia utility multipliers or comorbidity costs) were varied in groups, when varying all inputs of that type was more logical than varying one alone. Parameter variation is detailed in Table 77. The impact on the incremental cost-effectiveness ratio from each one-way variation in a parameter are displayed as a tornado diagram in Figure 15.

Table 77 Parameter variations used in one-way deterministic sensitivity analysis

Variable	Input value	Lower value	Upper value
Discount rate: cost	3.5%	-20%	20%
Discount rate: outcome	3.5%	-20%	20%
Percent female	Paediatric 50% Adult 56%	-20%	20%
Baseline paediatric age	6	6	17
Baseline adult age	20	18	30
Setmelanotide response rate	Paediatric 86% Adult 47%	-20%	20%
Decrease in BMI-Z with setmelanotide	[redacted]	1	3
Decrease in BMI with setmelanotide	[redacted]	1	3
Caregiver utility decrement	Paediatric 0.1 Adult: 0.1	-20%	20%
Number of caregivers	Paediatric 2 Adult 1	-20%	20%
Treatment discontinuation	1%	0%	5%
SMR for setmelanotide	0.85	0.5	1
BBS QALY multiplier	0.8	-20%	20%
Setmelanotide QALY multiplier	1	-20%	20%
Setmelanotide unit cost	Commercial in confidence data removed	-20%	20%
Setmelanotide monitoring cost	66.19	-20%	20%
BSC monitoring cost	183.88	-20%	20%
Hyperphagia utility multiplier	Multiple values	-20%	20%
BMI-related healthcare costs	Multiple values	-20%	20%
Early-onset obesity SMRs by BMI	Multiple values	-20%	20%
Comorbidity disutilities by BMI	Multiple values	-20%	20%
Comorbidity costs by BMI	Multiple values	-20%	20%
Baseline BMI category	Multiple values	100% 20 to 25	100% 40+
Baseline BMI Z-score category	Multiple values	100% 0 to 1	100% 4+
Hyperphagia treatment effect	Multiple values	50% moderate	100% mild
Baseline hyperphagia category	Multiple values	100% mild	100% severe

Figure 15 One-way deterministic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide treatment in paediatric patients with BBS



B.3.10.3 Scenario analysis

Multiple scenario analyses were considered to explore the effect of varying certain inputs or the addition of model parameters.

B.3.10.3.1 Uniform baseline BMI Z-score distribution

A uniform baseline distribution of paediatrics patients across BMI Z-score categories was considered, to provide insight into the change in outcome when baseline patient distribution differs from that observed in the clinical trial. The same number of patients as in the clinical trial (16 paediatric patients) were redistributed amongst starting BMI Z-score categories: no patients were assumed as being at the two lowest BMI Z-score levels (0 to <1 and 1 to <2); with patients distributed evenly across the five remaining categories (20% of patients each with BMI Z- scores of 2.0 to <2.5, 2.5 to <3.0, 3.0 to <3.5, 3.5 to <4.0, and ≥4.0).

B.3.10.3.2 Increasing best supportive care costs for increasing obesity level

As there is potential for physician visits and resource use to increase as BMI/BMI Z-score increases, the change in outcome associated with increasing BSC monitoring

costs with increasing BMI/BMI Z-score was assessed. It was assumed that the cost for the lowest BMI/BMI Z-score subgroups was consistent with the base case, with an additional £25 added for each increase in BMI/BMI Z-score category (Table 78).

Table 78 Increasing best supportive care monitoring costs with increasing BMI/BMI Z-score category for scenario analysis

BMI/BMI Z-score category	Cost
BMI 20 to <25 kg/m^2 BMI Z-score 0.0 to <1.0	£183.88
BMI 25 to <30 kg/m^2 BMI Z-score 1.0 to <2.0	£208.88
BMI 30 to <35 kg/m^2 BMI Z-score 2.0 to <2.5	£233.88
BMI 35 to <40 kg/m^2 BMI Z-score 2.5 to <3.0	£258.88
BMI 40 to <45 kg/m^2 BMI Z-score 3.0 to <3.5	£283.88
BMI 45 to <50 kg/m^2 BMI Z-score 3.5 to <4.0	£308.88
BMI ≥50 kg/m^2 BMI Z-score ≥4.0	£333.88

B.3.10.3.3 Decreasing comorbidity disutilities by 10%

Disutility values for each comorbidity were reduced by 10% as shown in Table 79 to assess the impact of varying their magnitude on the model.

Table 79 Reduced comorbidity disutility values tested in scenario analyses

BMI Z-score	Sleep apnoea	Osteoarthritis	NASH	T2DM	Cardiovascular events
0.0 to <1.0	0.000	0.000	0.000	0.000	0.000
1.0 to <2.0	0.020	0.056	0.000	0.023	0.030
2.0 to <2.5	0.024	0.088	0.000	0.029	0.040
2.5 to <3.0	0.029	0.139	0.000	0.036	0.054
3.0 to <3.5	0.035	0.219	0.000	0.045	0.073
3.5 to <4.0	0.042	0.346	0.000	0.057	0.098
≥4.0	0.052	0.546	0.000	0.072	0.132

B.3.10.3.4 Decreasing utility scores for severe obesity

The change in outcome as a result of decreasing the utility for patients with severe obesity was explored, with the utility value for patients with BMI ≥50 kg/m^2 or BMI Z-score ≥4 decreased by an additional 0.05, resulting in the utility values shown in Table 80.

Table 80 Utility values for patients with severe obesity for use in scenario analysis

Age group	Utility value
18 to 30 years	0.75
31 to 40 years	0.72
41 to 50 years	0.65
51 to 60 years	0.64
61 to 70 years	0.61
>70 years	0.61

B.3.10.3.5 Discount rate for benefits 1.5%

The impact of a 1.5% discount rate for benefits on model outcomes, instead of the 3.5% discount used in the base-case, was assessed.

B.3.10.3.6 Lower hyperphagia treatment effect

The potential for a lower setmelanotide effect on hyperphagia was assessed by assuming that symptom severity for 50% of treatment responders reduced to mild hyperphagia and for the other 50% of treatment responders to moderate hyperphagia.

B.3.10.3.7 Caregiver productivity cost

The impact of caring for a BBS patient on caregiver productivity, seen as absenteeism, was assessed. CARE BBS 2022 data show that the average BBS patient carer is unable to attend work for 17% of the time. Assuming a median wage-rate in the UK of £13.58 per hour, an 8-hour working day, 5 working days per week, and 52 working weeks a year, this equates to a per-carer cost of £4,833.67. The cost to carers associated with absenteeism was tested in the model.

The results of the seven scenario analyses are presented in Table 81.

Table 81 Effect of scenario analyses on incremental cost-effectiveness ratio for setmelanotide treatment in paediatric patients with BBS

Scenario	ICER (£/QALY)
Uniform baseline BMI/BMI Z-score category distribution	£196,059
Increased BSC costs by £25 for increasing obesity level	£191,020
Comorbidity disutilities decreased by 10%	£193,874
Severe obesity utility decreased by 0.05	£191,351
1.5% discount rate for benefits	£129,259
Reduced hyperphagia treatment effect	£219,668
Caregiver productivity cost	£179,295

B.3.11 Subgroup analysis

An additional analysis considered the adult population. Although in future most BBS patients will start setmelanotide treatment as children, the current population of BBS patients with hyperphagia and obesity also includes adults. An analysis was, therefore, conducted to reflect the current setmelanotide-treatable population, which comprised 60% paediatric patients and 40% adult patients.

Adult baseline BMI categorisation reflected trial data in which: [redacted]%of patients were of BMI category 30 to <35 kg/m^2; [redacted]%were 35 to <40 kg/m^2; [redacted]%were 40 to <45 kg/m^2, [redacted]%were 45 to <50 kg/m^2, and [redacted]%were ≥50 kg/m^2. Adult treatment response was defined as ≥10% weight loss from baseline to the 52-week follow-up. This definition resulted in a response rate of 46.7%, with adult responders improving an average of one BMI category according to clinical trial data. Cost-effectiveness analysis data for the adult population are presented in Table 82 and for the current treatable population in

Table *83*.

Table 82 Cost-effectiveness analysis results for setmelanotide in adult patients with BBS

	Setmelanotide	Best supportive care
Total cost	Commercial in confidence data removed	£125,914
Total life-years gained	Commercial in confidence data removed	20.71
Total quality-adjusted life years	Commercial in confidence data removed	0.56
Total undiscounted quality-adjusted life years	Commercial in confidence data removed	0.97
Incremental costs	Commercial in confidence data removed	
Incremental life years gained	Commercial in confidence data removed	
Incremental quality-adjusted life years	Commercial in confidence data removed	
Incremental undiscounted quality-adjusted life years	Commercial in confidence data removed	
Incremental cost-effectiveness ratio	£218,864/QALY	

Table 83 Cost-effectiveness analysis results for setmelanotide in the BBS treatable population (60% paediatric and 40% adult patients)

	Setmelanotide	Best supportive care
Total cost	Commercial in confidence data removed	£117,528
Total life-years gained	Commercial in confidence data removed	22.75
Total quality-adjusted life years	Commercial in confidence data removed	0.76
Total undiscounted quality-adjusted life years	Commercial in confidence data removed	2.09
Incremental costs	Commercial in confidence data removed	
Incremental life years gained	Commercial in confidence data removed	
Incremental quality-adjusted life years	Commercial in confidence data removed	
Incremental undiscounted quality-adjusted life years	Commercial in confidence data removed	
Incremental cost-effectiveness ratio	£198,081/QALY	

B.3.12 Benefits not captured in the QALY calculation

Most cost and health outcomes relevant to the decision problem are captured in the economic analysis. Costs associated with management of obesity due to BBS are typically borne by the NHS. However, obesity can also have financial implications for patients, being associated with work absenteeism and presenteeism and permanent work loss. Employed obese people generally have significantly higher indirect costs (absenteeism, short- and long-term disability etc.) compared with employed non-obese individuals (Goettler 2017). An EU5 study into the humanistic and economic burden of increasing BMI found that obese respondents had significantly greater absenteeism and presenteeism than non-obese respondents, which was associated with almost €2,000 more in indirect costs for those of BMI ≥40 kg/m^2 (Gupta 2015).

The main costs incurred by patients and carers are those associated with travelling to specialist BBS appointments at centres in Birmingham or London. Some patients may have to travel a significant distance to attend, and an overnight stay may be necessary which is associated with additional costs not reimbursed by the NHS. In addition given the prevalence of hyperphagia in BBS patients, it can be assumed

that patients or their carers will spend significantly more on food than other patient groups.

No studies have evaluated the time spent by family members providing care for a patient with BBS. However, given the severity of the condition and its associated complications, it is reasonable to assume that one parent may have to work part-time or even give up their job to provide care for a child with BBS.

Treating obesity in BBS patients may also have other health benefits that it has not been possible to quantify in the model. Treating the hyperphagia and obesity may make the overall patient management easier and thus the management of other co-morbidities related to BBS.

In terms of comorbidities directly related to obesity, we have not included the impact of dyslipidaemia, anxiety and depression, or polycystic ovary syndrome on quality of life.

B.3.13 Validation

The economic model was externally validated following the TECH-VER checklist, an accepted validation guideline (Büyükkaramikli 2019). Model validation included checking calculations and features for consistency and face validity, detailed checks on formulae, and assessment of validity of model functionality and macros. Thus, the review included black- and white-box testing. Event/state calculations, result calculations, uncertainty analysis, and overall tests of model functionality, transparency and validity were performed. As some additional changes were made to the model after validation, repeat internal and external model validations were conducted to reassess all updated model functionality and equations.

B.3.14 Interpretation and conclusions of economic evidence

This analysis clearly shows the significant quality of life benefits that can be achieved with setmelanotide treatment in an obese paediatric BBS population. With incremental QALYs of Commercial in confidence data removed compared with BSC alone, setmelanotide has the potential to improve the lives of BBS patients and their caregivers.

With an undiscounted QALY gain of Commercial in confidence data removed, setmelanotide would qualify for a willingness-to-pay threshold of £222,900 according to NICE HST cost-effectiveness guidelines. This analysis shows that setmelanotide falls comfortably under this threshold with an incremental cost-effectiveness ratio of £191,759. Multiple scenario analyses show further potential benefit for setmelanotide treatment, including one considering caregiver productivity costs in which setmelanotide could save over £4,000 per year in absenteeism alone.

The findings of this economic evaluation are unique for setmelanotide in this indication. The base-case results are specific to the paediatric population, as it is expected that the future population will mainly consist of paediatric patients identified by screening and genetic testing that promotes early BBS diagnosis. However, the current treatment-eligible BBS population includes adults. Despite the greater incremental cost-effectiveness ratio estimated for the adult population, the significant HRQoL benefits associated with setmelanotide make the treatment desirable for patients of all ages.

This evaluation is limited by the low number of BBS patients and resulting small clinical study patient cohorts; this results in large-range confidence intervals, a lack of BBS population-specific data, and potential for variable data interpretation. In addition hyperphagia severity is difficult to define, creating uncertainty in its impact on quality of life. Clinical experts agree that hyperphagia is not adequately captured by EQ-5D and so patient reported outcomes from the clinical trial were not used; rather, proxy data were included to estimate quality of life.

The strength of the economic model is its simplicity, comprising a simple life-table model that does not attempt to mimic BBS disease biology. With this approach, the life courses of BBS patients can be represented with flexibility using modifiable mortality parameters. In the future, the cost-effectiveness model could be updated using long-term, real-world data to populate existing parameters and allow the impact of setmelanotide to be clearly demonstrated.

B.3.15 Cost to the NHS and personal social services

It is anticipated that approximately Commercial in confidence data removed people with BBS will be eligible for setmelanotide treatment in England based on the full

marketing authorisation. Of these Commercial in confidence data removed are estimated to have severe hyperphagia (the subgroup for which NICE approval is sought). The eligible population was calculated as follows:

- It was estimated that there are 560 people with BBS in the UK (data from communication with BBS UK), equating to 472 people in England.
- 72% to 92% of BBS patients are obese (Forsythe 2013)
- 80% of BBS patients have had their diagnosis genetically confirmed, as required by the setmelanotide licence (Forsythe 2013)
- 20% of BBS patients have chronic renal failure and are therefore unlikely to receive setmelanotide treatment (estimate from treatment centres)
- The setmelanotide licence applies to patients over aged >6 years (estimated at 95% of patients by treatment centres)
- The NICE submission will seek reimbursement for BBS patients with severe hyperphagia only. It is estimated that approximately 60% of obese BBS patients have severe hyperphagia (KOL opinion)

Rhythm estimates that Commercial in confidence data removed patients will receive setmelanotide in Year 1, Commercial in confidence data removed patients in Year 2, Commercial in confidence data removed patients in Year 3, Commercial in confidence data removed patients in Year 4 and Commercial in confidence data removed patients in Year 5. It is expected that this will comprise approximately Commercial in confidence data removed paediatric patients and Commercial in confidence data removed adults, in line with the current BBS population. However, once the current adult population is treated it is expected that almost all future patients will start setmelanotide treatment in the paediatric setting.

The cost of setmelanotide is Commercial in confidence data removed per mg (PAS price). Average daily doses were calculated using data from Study RM-493-023.

- The first year per patient cost for a paediatric patient with BBS is Commercial in confidence data removed based on an average daily dose of Commercial in confidence data removed; the subsequent per patient yearly cost for a paediatric patient with BBS is Commercial in confidence data removed based on an average daily dose of Commercial in confidence data removed.

- The first year per patient cost for an adult with BBS is Commercial in confidence data removed based on an average daily dose of Commercial in confidence data removed; the subsequent per patient yearly costs for an adult with BBS is Commercial in confidence data removed based on an average daily dose of Commercial in confidence data removed.

It was assumed that there would be no cost associated with best supportive care and no additional resource use for either setmelanotide or best supportive care was included in budget-impact calculations. The net budget impact is estimated at:

Year 1 - Commercial in confidence data removed

Year 2 - Commercial in confidence data removed

Year 3 - Commercial in confidence data removed

Year 4 - Commercial in confidence data removed

Year 5 - Commercial in confidence data removed

The main limitations of the budget impact calculation are estimated patient numbers and estimates of average daily dose.

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B.5 Appendices

Appendix C1.1: Setmelanotide Summary of Product Characteristics

Appendix C1.2: UK Setmelanotide Public Assessment Report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Data analyses for all BBS patients enrolled in Study RM-493-022

Appendix N: Summary of Study RM-493-014

Appendix O: Vignette study assessing the utilities associated with hyperphagia

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome ID3947

Summary of Information for Patients (SIP)

January 2023

File name	Version	Contains confidential information	Date
ID3947 setmelanotide BBS_SIP	1.0	Yes	18th January 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Setmelanotide (IMCIVREE)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Patients with Bardet-Biedl syndrome (BBS) that has been confirmed by a genetic test who are obese and whose hunger and eating behaviour severely impact on their quality of life.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Setmelanotide is licenced for use as a treatment for obesity and to control hunger in adults and children aged 6 years or older who have genetically-confirmed BBS. It is to be used alongside advice to limit food intake and increase the amount of exercise of the person with BBS. It was approved for use in the UK by the Medicines and Healthcare Regulatory Agency (MHRA) on 17th November 2022.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Sponsorship of BBS UK Congress 2022, sum of £7,000. Rhythm Pharmaceuticals had no input into the agenda of the meeting.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

BBS is a rare disease that affects about 1 in 100,000 people in the UK (1). People with BBS often have a condition known as hyperphagia that causes them to become preoccupied with food. It is thought that hyperphagia is caused by an error in the brain pathway responsible for hunger and energy expenditure (2). The error prevents messages being sent to tell your body that it is not hungry. This leaves patients with feelings of extreme hunger (like starvation) and when they do eat it takes longer for them to feel full. Hyperphagia symptoms range from mild to severe. Patients with severe hyperphagia almost never feel full after a meal, overeat to the point of discomfort at most meals, try to sneak food almost every day and eat during the night most nights. These behaviours can have a big impact on the individual's quality of life limiting their ability to fully take part in school or work and social activities.

Patients with BBS may also have other symptoms such as sight problems/blindness, learning difficulties, hearing loss, speech problems, kidney problems, genital abnormalities, and can be born with an extra finger or toe. Some patients with BBS have some of these symptoms, while others have none. UK experts think that life expectancy for someone with BBS may be about 10 years shorter than for someone without BBS. Patients with severe disease need lifelong care, while those with milder symptoms can often complete school, find a job and live on their own.

Caring for a child with BBS and hyperphagia is difficult, particularly when trying to limit food intake and manage behaviour. Parents also feel blamed for over feeding (3), though they often try many ways of reducing their child's eating including locking up food. Managing food intake affects the relationships of the carer with the BBS patient and with other family members and makes going to social events difficult. Carers report that their child's uncontrollable hunger affects their own sleep, mood, work, and leisure or recreational activities.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

BBS is diagnosed based on its clinical symptoms, which are described as primary or secondary. Four primary symptoms or three primary symptoms with two secondary symptoms need to be present for someone to be diagnosed with BBS (4).

Primary symptoms	Secondary symptoms
• Rod-cone dystrophy (a disorder of the retina in the eye which eventually leads to blindness) • Polydactyly (extra fingers or toes) • Obesity • Genital abnormalities • Renal (kidney) abnormalities • Learning difficulties	• A delay in starting to talk • Delays in developing • Diabetes (high levels of sugar in the blood) • Abnormalities in the teeth • Congenital heart disease (abnormalities in the heart at birth) • Brachydactyly (short fingers or toes)/ syndactyly (webbed fingers or toes)

	• Ataxia (poor coordination) • Anosmia (no sense of smell)

Following clinical diagnosis, BBS is usually confirmed using genetic tests (5).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment of BBS involves managing the symptoms that are present, and so patients need support from different clinical specialists depending on their individual symptoms (6). In the UK people with BBS are assessed once a year by a team of clinical specialists based in Birmingham or London. The team works together to manage the different medical problems the person with BBS has, and may refer them back to their usual doctor for day-to-day care or onto another specialist if needed.

No drug treatments are currently available to manage hyperphagia and obesity in people with BBS. Obesity symptoms are currently managed by changing the diet (to reduce calorie intake) and increasing the amount of exercise a person with BBS takes. This can be effective for managing weight, which is important as excess weight can lead to the development of other diseases such as diabetes, high blood pressure and high blood cholesterol levels (4). However, weight management does not reduce the extreme hunger that makes the patient want to overeat. Setmelanotide (IMCIVREE) is the first treatment with the potential to reduce feelings of hunger and target the underlying cause of obesity in people with BBS.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The manufacturer of setmelanotide (Rhythm Pharmaceuticals) conducted a study of 242 adult carers of people with BBS, obesity and hyperphagia from the UK, US, Canada and Germany (7). Carers were asked to fill in a questionnaire that asks about: how often the person with BBS has hunger symptoms, how much hunger symptoms affect the person with BBS, how much the hunger of the person with BBS affects the carer, and the effect of weight on the person with BBS's quality of life (looking at their physical comfort, body esteem, social life, and relationships with family members).

Carers reported many problem behaviours due to uncontrollable hunger (hyperphagia) such as asking for extra food, eating very quickly, sneaking food, waking up looking for food at night, and asking for more food just after eating. They also reported that hunger affected the person's focus at school and some children missed school days due to BBS. Other problems were disrupted sleep, changeable mood and emotions, disrupted leisure activities, and issues with friends and family. Almost all carers reported problems with their child due to hunger in at least one of these areas over the preceding week.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

There are currently no treatments for BBS that tackle the underlying defect in the pathway responsible for controlling hunger that causes people with BBS to over-eat and therefore become obese. Setmelanotide works by restoring activity in the pathway so that signals can be sent to the brain to reduce hunger and increase energy expenditure. In this way, setmelanotide makes it easier for patients to lose weight when the patient is also ensuring they eat a healthy diet and get enough exercise.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Setmelanotide will not be used in combination with any other medicines for weight loss. Setmelanotide will be used alongside limiting food intake and increasing the amount of exercise in people with BBS, to encourage weight loss.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Setmelanotide is a potentially life-long treatment that is injected once a day, at the start of the day. Setmelanotide is injected at home by the patient or their carer under the skin of the stomach, thigh, or arm (at a different position each day). Before starting treatment, patients/ carers are taught how to inject setmelanotide correctly. Setmelanotide is injected at a dose of 1 mg, 2 mg or 3 mg a day in adults aged 16 years or older. The starting dose is 2 mg once a day given for 2 weeks. If the patient doesn't experience bothersome side effects, the dose can be increased to 3 mg once a day. If any dose causes side effects, the dose can be reduced to the next lower dose; if the reduced dose is tolerated, the dose can be increased again to the next dose up. Setmelanotide is injected at a dose of 0.5 mg, 1 mg, 2 mg or 3 mg a day in children aged from 6 to less than 16 years. The starting dose is 1 mg once a day given for 1 week. If the patient isn't bothered by side effects, the dose can be increased to 2 mg once a day for the next week. If the patient still isn't bothered by side effects, the dose can be further increased to 3 mg once a day. The 1 mg starting dose can be reduced to 0.5 mg once a day if the patient has side effects; if the reduced dose is tolerated, the dose can be increased again.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Two clinical trials provide data on the efficacy of setmelanotide in people with BBS. <u>Study RM-493-023</u> In Study RM-493-023, 44 BBS patients (in the US, Canada, the UK, France, and Spain) were assigned to receive an injection containing setmelanotide (22 patients) or an identical-looking injection containing no SETMELANOTIDE (placebo, 22 patients) for 14 weeks. Patients/carers and study staff did not know which patients received setmelanotide and which received the placebo injections. The aim of the first 14 weeks of the study was to test whether setmelanotide was better than placebo at managing hunger and inducing weight loss. After 14 weeks, 32 patients continued in the study, in which all patients (including those who received placebo for the first 14 weeks) received setmelanotide for 52 weeks. After 52 weeks of treatment with setmelanotide the trial assessed the proportion of patients aged 12 and over who lost at least 10% of their body weight. Patients entering the study were aged 6 years or older, had a clinical diagnosis of BBS and were obese. The study could also include patients with another disease affecting hunger, called Alström syndrome, but these patients are not included in the information presented in this submission. The last patient completed the study on 08 March 2021. Further information on Study RM-493-023 is presented in five reports (8, 9, 10, 11, 12).

Study RM-493-022

Study RM-493-022 included 42 patients with BBS (in the US, Canada, the UK, France, and Spain) who had completed other trials using setmelanotide. The aim of the study was to provide further data on the use of setmelanotide for up to 2 years.

Patients entering the study were aged 6 years or older. As well as patients with BBS this study also included patients with other diseases affecting hunger, but only information from patients with BBS is presented in this submission. Patients received setmelanotide (1 mg, 2 mg or 3 mg) once a day given as an injection under the skin at the same dose as they received in their previous trial.

Study RM-493-022 is still running. The information presented here dates from 29 October 2022 and includes data on 30 BBS patients who were assessed as having lost a meaningful amount of weight after taking setmelanotide for 52 weeks in a previous clinical trial. Further information on Study RM-493-022 is reported in (13).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Study RM-493-023

Please see Table 24, Table 25 and Table 26 of the submission for results from the first 14 weeks of Study RM-493-023.

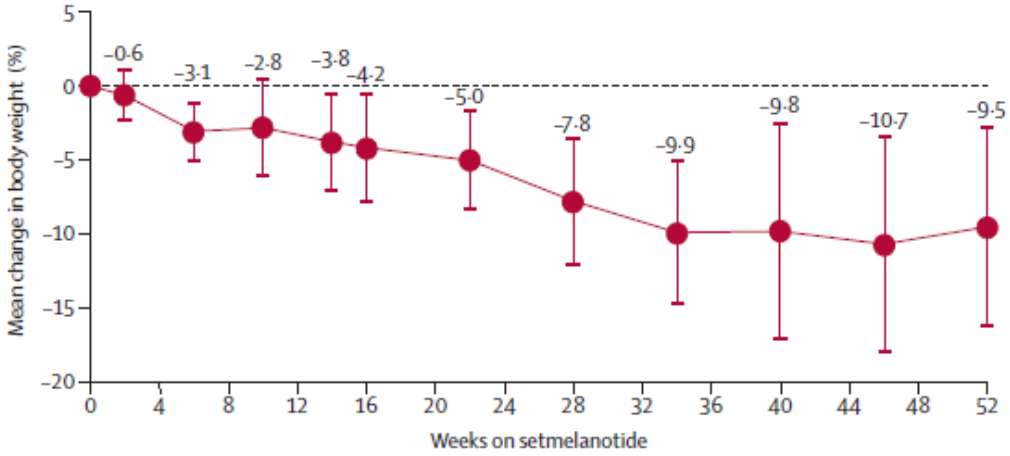
After 52 weeks of treatment with setmelanotide, 36% of patients with BBS aged 12 years or older and 47% of those aged 18 years or older had at least a 10% reduction in body weight.

- Patients aged 18 years or older lost an average of 9.4 kg in weight and their BMI reduced by 4.2 kg/m^2.
- Patients aged less than 18 years had an average reduction in BMI of 3.4 kg/m^2 and 0.8 reduction in BMI-Z score (the BMI assessment used for younger children).
- Worst/most hunger score was reduced by an average of 31% across all age groups.

Weight loss

The average change in body weight from the start of setmelanotide treatment in patients aged 18 years or older is shown in Figure 1. An average weight loss of 9.42 kg represents a change of almost 8% (5% is recognised as meaningful for clinical studies).

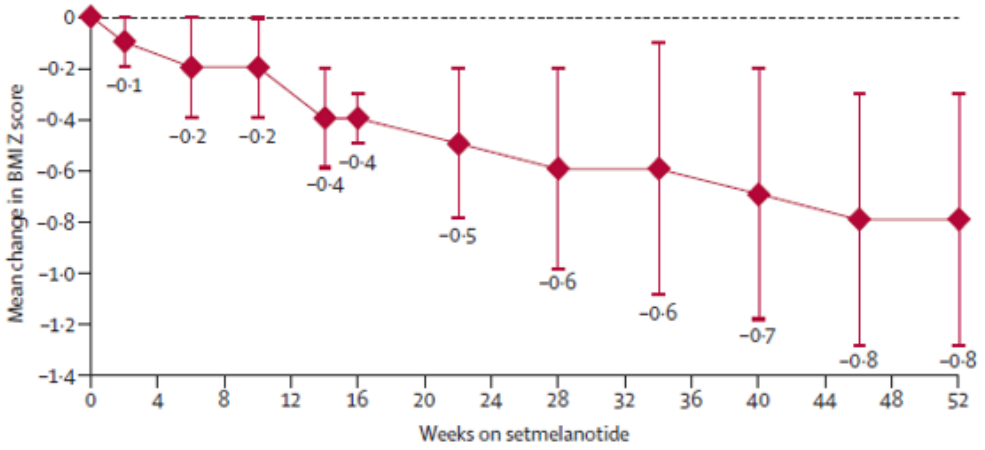
Figure 1 Average change in body weight during treatment with setmelanotide in patients with BBS aged 18 years or older



Body mass index

All but 2 patients having setmelanotide for 52 weeks had a reduction in BMI. Patients younger than 18 years were assessed using the BMI-Z score which is more suited to children. The average reduction of 0.8 points in BMI-Z score after 52 weeks is much greater than that reported to be meaningful to patients (0.15 to 0.20). The change in BMI-Z score for patients aged less than 18 years having setmelanotide over the course of the study is shown in Figure 2.

Figure 2 Average change in BMI-Z score from the start of setmelanotide treatment in patients with BBS aged less than 18 years

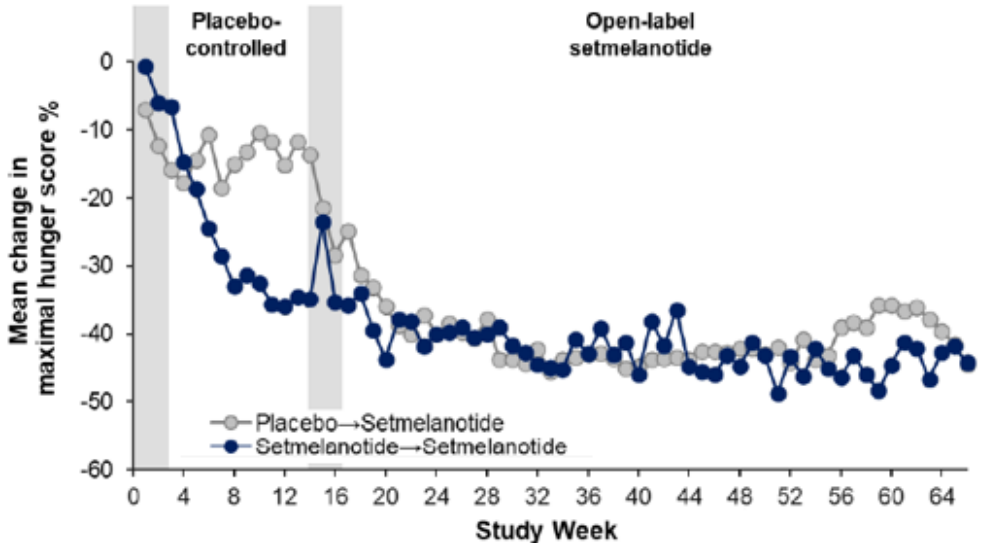


Overall, 86% of patients aged less than 18 years had a reduction of at least 0.2 in BMI-Z score by 52 weeks and 71.4% had a reduction of at least a 0.3.

Hunger score

The change in hunger score over 24 hours for patients having setmelanotide over the course of the study is shown in Figure 3.

Figure 3 Average change in worst/most hunger score during treatment with setmelanotide in patients with BBS aged 18 years or older



Patients had an average weekly reduction in most/worst hunger of 2.12 points on a 10-point scale, which is recognised as a meaningful reduction. Over half of patients (57%) had their hunger score reduced by a quarter during setmelanotide treatment. The aim of treatment is to reduce the level of hunger so that patients do not want to eat after finishing a meal. Having some level of hunger is needed for the patient to want to eat at mealtimes.

In line with the changes in body weight and BMI, over 52 weeks of setmelanotide treatment, patients had an average loss of 5.6 kg body fat though the amount of muscle did not change much (a loss of 1.2 kg). The average level of low-density lipoprotein (bad) cholesterol was reduced by 7.8%. The average level of high-density (good) cholesterol increased by 5.3%. The average waist circumference reduced by 7.2 cm.

Limitations of the study

After 14 weeks of treatment the study included only patients who received setmelanotide. Without a group of patients receiving a placebo, it is not possible to determine how much of the improvement in weight was due to setmelanotide and how much was due to the placebo effect (a phenomenon where a patient's symptoms improve because they believe they are receiving treatment) or the Hawthorne effect (a phenomenon where a person alters their behaviour because they are aware of being observed).

Measuring weight-related parameters in children and adolescents who are still growing and developing is difficult as these patients would be expected to show natural and healthy increases in weight and BMI as they grow. The measure of BMI-Z was developed to try to account for these natural increases and so BMI-Z results may be a better way of measuring obesity in children and adolescents.

Study RM-493-022

Please see section B.2.6.2 of the submission for results from Study RM-493-022.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

After 52 weeks of treatment with setmelanotide in Study RM-493-023, most patients reported improvements in or maintained their quality of life.

Of BBS patients aged 18 years or older who provided enough information (11 patients), the average quality of life score before starting setmelanotide treatment was 74.9 (the maximum score possible is 100) using IWQOL Lite which measures the effect of weight on quality of life. This indicates moderately reduced quality of life, with the score being lower than that seen in similar non-obese people (an expected score of 94.7, (14)). Treatment with setmelanotide for 52 weeks increased IWQOL Lite score by an average of 12 points, which is considered clinically meaningful (14). The greatest improvements related to areas of physical function and public distress.

Another quality of life questionnaire (EQ-5D-5L) was used in patients with BBS aged 16 and older. It also showed that quality of life scores in BBS patients before the start of the study were lower than in people without BBS. Treatment with setmelanotide increased average quality of life scores, with most effect seen for mobility and day-to-day activity.

Of BBS patients aged less than 18 years who provided sufficient information (9 patients), the average paediatric quality of life total score (PedsQL) before starting the study was 67.2, which is lower than seen in non-obese children (an expected score of 83.0, (15)). A paediatric score of 68.2 or lower indicates impaired quality of life. Treatment with setmelanotide for 52 weeks resulted in an average 11.2 point improvement in score. An increase of 4.4 points shows clinically meaningful improvement (16).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In Study RM-493-023, side effects seen with setmelanotide that did not occur with placebo were darkening of the skin, redness at the injection site, nausea (feeling as though you are going to vomit) and vomiting. Nausea was mostly mild and got better after the first few weeks of treatment. Two patients taking setmelanotide withdrew from the study due to adverse events that began after receiving treatment; one withdrew due to hot flashes, nausea, headaches, vomiting, and abdominal pain; the other withdrew due to nausea and vomiting.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Setmelnaotide is an effective treatment of obesity and hyperphagia in people with BBS, as it reduces hunger symptoms and body weight. During the first 14 weeks of Study RM-493-023, patients receiving setmelanotide had greater reductions in hunger, body weight and BMI than

those receiving placebo. Reductions in hunger were maintained over 52 weeks of setmelanotide treatment and weight loss also continued. Improvements were also seen in quality of life, and blood cholesterol and waist circumference was reduced.

The long-term extension study in which BBS patients received up to 2 additional years of setmelanotide treatment (3 years total) showed that the effect on weight and BMI could be maintained in patients who responded to setmelanotide treatment.

Setmelanotide has been shown to be safe with the main side effects being darkening of the skin, injection site reactions and nausea.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The disadvantages seen with setmelanotide treatment are minor and relate to side effects, such as darkening of the skin and injection site reactions. Nausea is also seen but is generally mild and usually gets better after the first few weeks of treatment.

Setmelanotide is given by an injection given each day but this can be done at home by the patient or carer.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- The model reflects the impact of having BBS with hyperphagia and obesity on quality of life. Patients enter the model at their current BMI/BMI-Z and hyperphagia level and are assigned a quality of life score depending on the severity of their condition (higher BMI/BMI-Z and more severe hyperphagia correspond to a worse quality of life). Costs are also assigned to the patient depending on the treatment they are receiving (setmelanotide in combination with

diet and exercise advice or diet and exercise advice alone). As time progresses, patients BMI/BMI-Z and hyperphagia can increase or decrease or remain the same, depending on the treatment they are receiving.

Modelling how much a treatment extends life

- No trial data was used to estimate how much setmelanotide extends life as the trials did not assess this. Instead, data from the literature was used to estimate the effect based on reductions in BMI/BMI-Z score.
- People with a higher BMI/BMI-Z score have a higher risk of death so setmelanotide is expected to extend life by decreasing BMI/BMI-Z score. In addition, setmelanotide is expected to reduce the impact of other diseases associated with obesity such as diabetes, hypertension and non-alcoholic fatty liver disease, which may also contribute to extending life.

Modelling how much a treatment improves quality of life

- Setmelanotide improves quality of life by reducing hyperphagia, a condition which results in feelings of starvation, feeling hungry again shortly after eating and taking a longer time to feel full. Patients enter the model with severe hyperphagia, which is assumed to improve to mild hyperphagia following treatment with setmelanotide. Patients who receive just diet and exercise advice do not see any improvement in their hyperphagia.
- Treatment with setmelanotide also results in weight loss, improvement in BMI/BMI-Z score and reductions in obesity-related comorbidities, all of which have a positive impact on quality of life.
- Quality of life inputs for the model were obtained from literature and consisted of PedsQoL (mapped to EQ-5D scores) and EQ-5D scores for general obesity estimates. Hyperphagia-related quality of life was estimated in a vignette study – a study that asked members of the public to read a description of hyperphagia and to rate what it would be like to live with so that researchers could determine its impact on quality of life.

Modelling how the costs of treatment differ with the new treatment

- Setmelanotide is more expensive than current treatment, with daily injections leading to increased costs compared to the current regimen of diet and exercise.
- The injections will be administered in the patient's home either by the patient themselves or caregivers, there is no additional cost for administration.

Uncertainty

- The impact of setmelanotide on life expectancy is based on the assumption that setmelanotide will extend life due to reducing early onset obesity.
- Data on the impact of setmelanotide on hyperphagia is also lacking. It was therefore assumed that patients who responded to setmelanotide in terms of seeing a reduction in MI/BMI-Z also improved from severe hyperphagia to mild hyperphagia, under the assumption that a significant decrease in hyperphagia would be the catalyst for the resulting weight loss and BMI improvement.
- Alternative assumptions were tested and hyperphagia treatment effect had the biggest impact on the cost-effectiveness estimates.

Cost effectiveness results

- Please see section B3.9 of the company evidence submission for cost-effectiveness results.

Additional factors

- A major benefit not captured in the QALY calculation is the reduction in caregiver absenteeism and presenteeism. The productivity impact of caring for a BBS patient is extreme, and reductions in patient hyperphagia and obesity can reduce the burden on caregivers significantly.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Setmelanotide corrects the defects in the hunger pathway of patients with BBS that prevent signals being sent to tell the body that it is no longer hungry. This means that setmelanotide works by a new and innovative mechanism to manage appetite in BBS patients and help them to stop overeating. Setmelanotide is the only treatment that targets the hyperphagia experienced by BBS patients.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
The clinical data for setmelanotide suggest that it may be more effective when taken for the first time in childhood. This may be because children have not developed habits around over-eating and treating hyperphagia early prevents these habits from forming. There is, therefore, the potential to discriminate against adults with hyperphagia and obesity whose eating habits may mean that reductions in hunger do not always translate in such big reductions in weight. Whilst adults may not see the same extent of weight loss as children, they still have the potential to benefit from the improved quality of life as a result of reduced hyperphagia.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Great Ormond Street Hospital. Bardet-Biedl Syndrome clinical outcomes. https://www.gosh.nhs.uk/conditions-and-treatments/clinical-outcomes/bardet-biedl-syndrome-clinical-outcomes/ Accessed November 2022. UK for Bardet-Biedl syndrome service. NHS Commissioning Board 2013. https://www.england.nhs.uk/wp-content/uploads/2017/03/a17-bard-biedl-all.pdf Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Body mass index (BMI) - a person's weight in kilograms divided by the square of their height in meters. BMI is a screening method used to categorise low weight, healthy weight, overweight, and obesity.

BMI-Z score – used to calculate BMI of in people aged 2 to 20 years

EQ-5D-5L – a tool often used to measure quality of life in clinical trials

Hyperphagia is condition in which someone has extreme hunger, rarely feels full and is preoccupied with food.

Impact of Weight on Quality of Life-Lite (IWQOL-Lite) - a questionnaire that allows patients to report on their quality of life, that focuses on the effect of weight on quality of life

Nausea - feeling as if you are about to vomit

Paediatric quality of life (PedsQL) – a questionnaire that can be used to measure quality of life in healthy children and adolescents and those with health conditions

Placebo - a dummy treatment that looks and is used in the same way as setmelanotide. It is not possible for the patient/carer or study staff to tell the difference between placebo and setmelanotide.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

(1) Great Ormond Street Hospital. Bardet-Biedl Syndrome clinical outcomes. https://www.gosh.nhs.uk/conditions-and-treatments/clinical-outcomes/bardet-biedl-syndrome-clinical-outcomes/ Accessed November 2022.

(2) Pomeroy J, Krentz AD, Richardson JG, Berg RL, VanWormer JJ, Haws RM. Bardet-Biedl syndrome: Weight patterns and genetics in a rare obesity syndrome. Pediatr Obes 2021;16:e12703.

(3) BBS patient journey report. Data on file.

(4) Forsythe E, Kenny J, Bacchelli J, Beales PL. Managing Bardet-Biedl syndrome - now and in the future. Front Pediatr 2018;6:23.

(5) Mujahid S, Hunt KF, Cheah YS, et al. The endocrine and metabolic characteristics of a large Bardet-Biedl syndrome clinic population. J Clin Endocrinol Metab 2018;103(5):1834-1841.

(6) UK for Bardet-Biedl syndrome service. NHS Commissioning Board 2013. https://www.england.nhs.uk/wp-content/uploads/2017/03/a17-bard-biedl-all.pdf

(7) CARE-BBS study report. Caregiver burden in Bardet-Biedl syndrome (CARE-BBS): A survey of BBS-related obesity and hyperphagia impacts in the United States, United Kingdom, Canada, and Germany. 2022.

(8) Haqq AM, Chung WK, Dollfus H, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. Lancet Diabetes Endocrinol 2022;10(12):859-868.

(9) Argente J, Clément K, Dollfus H, et al. Phase 3 trial of setmelanotide in participants with Bardet-Biedl syndrome: placebo-controlled results. Hormone Res Paediatrics 2021;94:30-31.

(10) Haws R, Clement K, Dollfus H, Haqq A, Martos-Moreno G, Chung W, et al. Efficacy and safety of open-label setmelanotide in Bardet-Biedl syndrome: a Phase 3 trial. Obesity (Silver Spring, Md) 2021;29:12.

(11) Forsythe E, Haws, R, Argente, J, et al. Quality of life in patients with Bardet-Biedl syndrome in a setmelanotide Phase 3 trial. Obesity (Silver Spring) 2021;29150,257.

(12) Haws R, Clement K, Dollfus H, et al. Efficacy and safety of the melanocortin-4 receptor agonist setmelanotide in obesity due to Bardet-Biedl syndrome: A Phase 3 trial. Hormone Res Paediatrics. 2021;94:91.

(13) Argente J, Clement K, Chung WK, et al. Long-term efficacy of setmelanotide in patients with Bardet-Biedl syndrome. Endocrine Society annual meeting June 2022; Atlanta, GA.

(14) Crosby RD, Kolotkin RL, Williams GR. An integrated method to determine meaningful changes in health related quality of life. J Clin Epidemiol 2004;57(11):1153-1160.

(15) Schwimmer JB, Burwinkle TM, Varni JW. Health related quality of life of severely obese children and adolescents. JAMA 2003;289(14):1813-1819.

(16) Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3(6):329-341.

BRISTOL TAG

EVIDENCE FOR DECISION MAKERS

National Institute for Health and Care Excellence

Health technology evaluation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome ID3947

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
ID3947 Clarification Questions_responses_FINAL [no ACIC]v3.docx	1.3	No	7th July 2023

Note: This document contains the final responses to the clarification questions, and supersedes the First Draft of Responses shared on 24th of February. Questions with additional answers or changes to the answers since the draft version are identified herein in Green

Section A: Clarification on effectiveness data

Study Population

A1. Priority Question: The Executive Summary of the CS states that the submission is made for *"a subpopulation of BBS patients who are classified as having severe hyperphagia and obesity*" (pg 9, CS). The agreed scope for the decision problem does not focus on patients with "severe hyperphagia". Please can you justify the change in population, which now focuses on a subgroup of the original scope. In addition, we note that the inclusion/exclusion criteria for RM-493-023 and RM-493-022 do not include severity of hyperphagia and no detail is provided in the CS as to how the degree of hyperphagia severity was evaluated in participants. Please can you explain how hyperphagia severity was evaluated for participants in the RM-493-023 and RM-493-022 studies and provide study results by hyperphagia severity level for the primary endpoint and for BMI and BMIz at 52 weeks?

In the opinion of clinical experts, setmelanotide is most likely to be used in patients with severe hyperphagia who are also those experiencing the highest weight gain, and those who would experience the most benefits in terms of reducing the symptoms of severe hyperphagia, which include[1]:

- An overwhelming, heightened and relentless hunger mimicking feelings of starvation
- Longer time to reach satiety and shorter duration of satiety
- Severe preoccupation with food
- Persistent and potentially extreme food-seeking behaviours, such as night eating, stealing food and eating non-food items
- Distress or inappropriate behavioural response if denied food

Given the extremely negative impact of these severe hyperphagic behaviours on quality of life, and setmelanotide's ability to improve symptoms of hyperphagia, it was felt that restricting the submission to patients with severe hyperphagia was appropriate.

Hyperphagia severity of participants in RM-493-023 and RM-493-022 was not measured in the trials as no tool exists for measuring hyperphagia that is specific for BBS patients. Instead, hunger scores were captured. However, using extent of hunger in isolation is not an effective means of measuring hyperphagia, as symptoms of hyperphagia (outlined above) are more than feelings of hunger and overeating. For example, a patient with severe hyperphagia eating multiple times a day with regular snacking, may maintain a hunger level that appears moderate on a ten-point scale. After taking setmelanotide, their hyperphagia may reduce so that the same patient only needs to eat three meals a day to maintain a similar level of hunger. In addition, due to the genetic nature of the indication, patients have never experienced life without hyperphagia. Thus, they do not have a frame of reference to measure hunger. In patient exit interviews several patients quoted: *"I never knew what it was not to be hungry until I initiated treatment with setmelanotide".*

Thus, it is not possible to provide the results by hyperphagia severity and providing results by level of hunger at baseline is not relevant in the indication.

It was instead assumed that any patients who responded to setmelanotide, in terms of seeing a clinically meaningful reduction in weight/BMI/BMI-z over the duration of the trial, had entered the

trials with severe hyperphagia (the severe hyperphagia being the cause of their obesity) and that the weight response to setmelanotide was mediated through a reduction in hyperphagia severity. It was assumed that in order to lose the clinically significant amount of weight required to qualify as a 'responder' that hyperphagia severity was reduced from 'severe' to 'mild'.

A2. Priority Question: Table 12 in the CS reports the baseline characteristics for RM-493-023, by treatment arm, for the whole study sample (N=44). Please can you provide these patient characteristics by 'cohort' of RM-493-023 (i.e. by pivotal and supplemental participants) and by those participants with ⩾52 weeks follow up and participants with <52 weeks follow up.

Please see below:

	Setmelanotide		**Placebo**	
	(N=22)		**(N=22)**	
Cohort/ follow up:	Pivotal (n=16)	Supp (n=6)	Pivotal (n=16)	Supp (n=6)
Mean (SD) [range] age, years	[redacted]	[redacted]	[redacted]	[redacted]
≥18 years	[redacted]	[redacted]	[redacted]	[redacted]
≥12 to <18 years	[redacted]	[redacted]	[redacted]	[redacted]
<12 years	[redacted]	[redacted]	[redacted]	[redacted]
Female n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity				
Non-Hispanic and non-Latin	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic or Latin	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) [range] weight, kg	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) [range] BMI, kg/m	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged ≥12 years without cognitive impairment completing the daily hunger questionnaire, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most/worst hunger, mean (SD) [n]	[redacted]	[redacted]	[redacted]	[redacted]

Clarification Questions

	Setmelanotide		Placebo	
	(N=22)		(N=22)	
Cohort/ follow up:	<52 weeks follow up (n=8)	≥52 weeks follow up (n=14)	<52 weeks follow up (n=10)	≥52 weeks follow up (n=12)
Mean (SD) [range] age, years	[redacted]	[redacted]	[redacted]	[redacted]
≥18 years	[redacted]	[redacted]	[redacted]	[redacted]
≥12 to <18 years	[redacted]	[redacted]	[redacted]	[redacted]
<12 years	[redacted]	[redacted]	[redacted]	[redacted]
Female n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity				
Non-Hispanic and non-Latin	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic or Latin	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) [range] weight, kg	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) [range] BMI, kg/m	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged ≥12 years without cognitive impairment completing the daily hunger questionnaire, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most/worst hunger, mean (SD) [n]	[redacted]	[redacted]	[redacted]	[redacted]

A3. Priority Question: As patients registered on the CRIBBS database are used as an historical control for the 52-week follow-up in Study RM-493-023 please can the patient characteristics for this control group be provided. Please provide the information for the same characteristics as listed above in question A2. Were the CRIBBS data matched to the characteristics in RM-493-023? Were any of the patients contributing to the historical control group also enrolled in either study RM-493-023 or RM-493-014?

The CRIBBS registry is an open, enrolling international database designed to understand the longitudinal clinical outcomes in patients with BBS and is under the leadership of Dr. Robert Haws at the Marshfield Clinic in Marshfield, Wisconsin. Rhythm does not own or formally sponsor the CRIBBS registry.

Clarification Questions

Rhythm received deidentified individual body weight data from the CRIBBS registry, including longitudinal body weight records, from a total of [redacted] BBS patients, both children and adults ranging in age from 0 to 68 years. There were approximately equal numbers of male and female patients in this cohort.

Since Rhythm chose the population of patients ≥12 years old (to limit the effect of growth and development on detection of weight loss) for the primary endpoint, CRIBBS data were extracted for that specific population. [redacted] one-year periods for this analysis. For each patient, one or more years' worth of data records (ie, date of interview, age, height, weight and BMI) may have been available. No patient had more than four years of data.

Rhythm requested and received only the following limited data from the CRIBBS registry: patient ID number, genetic mutation, sex, year of birth, date of interview, height and weight and the derived variables of age and BMI. As a result, we cannot match patients from the CRIBBS analysis to patients entered in the trial.

The data in the CRIBBS registry were de-identified when received by Rhythm, and we have no way to know whether any patients with data in the registry also participated in the RM-493-023 clinical trial. It should also be noted that the analysis of CRIBBS patients was performed prior to start of trial recruitment thus it was not possible to match these patients to the trial patients.

A4. Priority Question: Table 13 in the CS shows baseline BMI and BMI Z-score categories for BBS patients. Please can you provide the data in Table 13 by treatment arms?

The table below shows the starting BMI and BMI-z score categories by treatment arms. Note that after 14 weeks of treatment all patients received setmelanotide until they had completed 52 weeks of treatment with setmelanotide.

Baseline BMI and BMI-z score categories for BBS patients (Study RM-493-023, pivotal patients SAS)

Baseline BMI (kg/m^2) / BMI-z score category	**BMI in BBS patients aged ≥18 years (N=16)**		**BMI-z score in BBS patients aged <18 years (N=16)**	
	Placebo (N=9)	**Setmelanotide (N=7)**	**Placebo (N=7)**	**Setmelanotide (N=9)**
BMI 20 to ≤25 BMI-z 1 to ≤ 2	[redacted]	[redacted]	[redacted]	[redacted]
BMI 25 to ≤30 BMI-z 2 to ≤2.5	[redacted]	[redacted]	[redacted]	[redacted]
BMI 30 to ≤35 BMI-z 2.5 to ≤3	[redacted]	[redacted]	[redacted]	[redacted]
BMI 35 to ≤40 BMI-z 3 to ≤3.5	[redacted]	[redacted]	[redacted]	[redacted]
BMI 40 to ≤45 BMI-z 3.5 to ≤4	[redacted]	[redacted]	[redacted]	[redacted]
BMI 45 to ≤50	[redacted]	[redacted]	[redacted]	[redacted]

Baseline BMI (kg/m²) / BMI-z score category	BMI in BBS patients aged ≥18 years (N=16)		BMI-z score in BBS patients aged <18 years (N=16)	
	Placebo (N=9)	Setmelanotide (N=7)	Placebo (N=7)	Setmelanotide (N=9)
BMI-z 4+				
BMI 50+	[redacted]	[redacted]	[redacted]	[redacted]

A5. On page 43 of the CS, it is noted that participants from both RM-493-023 and RM-493-014 were eligible for participation in RM-493-022. Table 1, Appendix M (reproduced below) provides the baseline characteristics for all participants recruited to the extension study (RM-493-022). Please could this information also be stratified by the two source/ index studies (RM-493-023 and RM-493-014) from which participants were recruited.

Thank you for your request. However, we are unable to provide this data at this stage.

	Total RM-493-022 (N=42)	Participants recruited from RM-493-023 (N=?)	Participants recruited from RM-493-014 (N=?)
Mean (SD) [range] age, years	[redacted]		
Female, n (%)	[redacted]		
Race, n (%)		Race, n (%)	
White	[redacted]		
Black or African American	[redacted]		
Asian	[redacted]		
Other	[redacted]		
Ethnicity, n (%)		Ethnicity, n (%)	
Non-Hispanic and non-Latin	[redacted]		
Hispanic or Latino	[redacted]		
Unknown	[redacted]		
Mean (SD) [range] weight, index study, kg	[redacted]		
Mean (SD) [range] weight, extension study, kg	[redacted]		
Mean (SD) [range] BMI, index study, kg/m²	[redacted]		
Mean (SD) [range] BMI, extension study, kg/m²	[redacted]		
Mean (SD) [range] BMI-z score, index study	[redacted]		
Mean (SD) [range] BMI-z score, extension study	[redacted]		

A6. For study RM-493-023, please can you confirm that only patients randomized after the protocol amendment (described on page 34 of CS as having been issued after the pivotal cohort had fully enrolled) are referred to as “supplemental patients"?

Yes, that is correct. Only patients randomised after the protocol amendment are referred to as supplemental patients.

A7. Please can you provide the reasons why “approximately 10%” of the BBS patients in Study RM-493-023 did not have their BBS diagnosis confirmed genetically?

Bardet Biedl Syndrome is usually diagnosed initially though the presence of clinical symptoms, then genetically confirmed through identification of a pathogenic or likely pathogenic variant in one of the known BBS genes.

A genetically confirmed diagnosis of BBS is defined as a biallelic (homozygous or compound heterozygous) loss-of-function mutation in BBS genes. The list of BBS genes is regularly expanding, with new genes classified as BBS genes and additional mutations regularly classified as loss-of function. BBS genetic diagnosis panels thus keep expanding to keep up with the identification and reclassification of novel BBS genes and mutations.

Genetic confirmation of BBS was not a formal inclusion criterion. As a result, some patients were included who had a clinical diagnosis of BBS but did not have genetic confirmation at time of inclusion. This does not mean that no mutation was present or identified, but rather that the mutation was either:

- Not detected by the BBS panel used at time of genetic diagnosis
- In a gene not yet identified as a BBS Gene

However, it should be noted that once 10% of patients without a confirmed BBS diagnosis had been enrolled in the trial, sites were notified that only genetically confirmed BBS patients could be enrolled. In addition, patients without a genetically confirmed BBS diagnosis had to be reviewed with the Sponsor’s medical monitor prior to enrolment.

Comparators/Interventions

A8. Priority Question: On page 38 CS states: “*During the study, conduct was changed to permit the use of GLP-1 receptor agonists and remove the prohibition on use of anorectic agents or drugs with anorexia as a non-rare side effect*.” Please provide details on the number of patients who received these additional drugs, including names of drugs, separately for:

a. the 14-week randomised period, for setmelanotide arm and placebo arm
b. the 52-week open label period

[redacted]

[redacted]

A9. Please could the company provide more detail on the placebo given to participants randomised to the control arm of the pivotal and supplemental cohorts of study RM-493-023. Please include details on what form the placebo took (e.g. a pill, an injection, other), whether participants given placebo followed a pseudo-titration regime and if so, was this to the same schedule as setmelanotide, following the same administration process, and clinic attendance pattern? Who was the placebo administered by and was this different from the setmelanotide arm? Did the type of placebo given vary by centre or by country?

The placebo, like setmelanotide was administered via subcutaneous injection QD in the morning. Both treatments were indistinguishable clear, colourless to slightly opalescent solutions essentially free of visible particulates. All investigational study drugs (setmelanotide and placebo) were supplied by the Sponsor and did not vary by centre or country.

The administration of placebo followed the same administration process and clinic attendance pattern as that of setmelanotide, following the below dosing schedule.

Study Week	Patients ≥16 years of age	Patients <16 years of age
1	2.0 mg or placebo	1.0 mg or placebo
2	2.0 mg or placebo	2.0 mg or placebo
3-14	3.0 mg or placebo	3.0 mg or placebo
15	2.0 mg	1.0 mg
16	2.0 mg	2.0 mg
17-66	3.0 mg	3.0 mg

There was extensive training of patients in drug administration including educational materials. Study specific training materials were provided to both the investigative staff and study participants and caregivers. Arrangements were to be made for those who were not able to successfully self-administer the study drug to have assistance by a visiting home healthcare practitioner. Patients and/or their caretakers (including home healthcare practitioners) were responsible for all procedures associated with study drug administration, i.e., drawing up and self-administering the study drug QD (including during the practice sessions).

A10. The CS indicates that setmelanotide should be prescribed concurrently with dietetic advice and exercise regimes. Were participants in studies RM-493-023 and RM-493-022 also receiving dietetic and exercise advice? If so, please provide details of what dietetic advice and exercise regimes were prescribed to participants, and whether this varied by age, BMI, severity of hyperphagia and/or trial centre.

The trial was designed to measure the effect of setmelanotide as a single variable on anthropometric criteria, hunger and QoL, in comparison with the baseline. Thus, in the trial, diet and exercise programs were not to be changed compared to what was used at time of inclusion. The only exception being paediatric patients, for whom nutritional counseling and monitoring were to be performed by an appropriate dietician or nutritionist (or equivalent), to ensure that paediatric patients have adequate nutritional/dietary intake to maintain proper growth and development, but not to increase weight loss.

However, in real life clinical practice we advocate setmelanotide to be used in combination with diet and exercise. Actually, we believe that the reduction in hyperphagia achieved with setmelanotide is key to the success of any dietary program, and that the initial weight loss due to the therapy can only facilitate the implementation of exercise programs.

As a result, the weight loss achieved in real life when therapy with setmelanotide is combined with successful diet and exercise, is expected to be greater than that shown in the trial where diet and exercise could not be adjusted.

A11. Please can you confirm if the patients forming the historical control group (CRIBBS database registry) had received, or were currently, receiving treatments that would have been ineligible for inclusion in study RM-493-023 and RM-493-014?

It is indeed likely that some of the patients included in the CRIBBS registry were receiving treatment that would have made them ineligible for inclusion in trials RM-493-023 and RM-493-014. Since CRIBBS is not a registry organized or owned by Rhythm, we do not have specific data on these treatments.

However, patients in CRIBBS responding to alternative treatments were included in the 10% corresponding to the null hypotheses. But patients not responding to these alternative therapies who can be considered as more challenging patients were candidates for inclusion in our trials.

Outcome definition

A12. Priority Question: Please can you provide evidence to support the validity and reliability of the hunger measurement score used for patients >12 years of age without cognitive impairment. If the scale has been validated in previous clinical studies, please can the company provide the supporting data to the EAG for review. Please also provide evidence that supports the use of the specific questions and 10-point Likert scale to reliably differentiate patients' severity of hyperphagia, such as to identify those who have severe hyperphagia.

Hunger scores were not used to differentiate between hyperphagia severity in this submission. Instead, all responder patients in the study were assumed to:

- Start the study with severe hyperphagia, based on the assumption that their severe obesity is the result of severe hyperphagia.

- Transition to mild hyperphagia following treatment with setmelanotide, based on the assumption that their clinically significant weight loss is due to a significant reduction in hyperphagia.

A13. The exploratory endpoints for study RM-493-023 outlined on page 39 of the CS were not pre-specified in the study protocol {Haws, 2021 #316}. At what stage of the study were these exploratory endpoints decided? Additionally, at what stage of the study were the exploratory endpoints implemented for study RM-493-022, listed on page 45 of the CS?

The Haws paper listed as reference does not include all the exploratory endpoints. Please find below tables detailing at which stage of the studies the exploratory endpoints were decided (RM-493-023) or implemented (RM-493-022).

Study stage at which exploratory endpoints were decided in study RM-493-023

Exploratory endpoint	**At which stage of study was it decided?**
The proportion of patients of any age who achieved a ≥10% reduction from baseline in body weight after ~52 weeks of treatment.	Pre-specified in study protocol as a key secondary endpoint. Later considered an exploratory endpoint.
The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% at 14 weeks.	Pre-specified in study protocol as a key secondary endpoint. Later considered an exploratory endpoint.
Composite response rate, defined as patients who achieved either a ≥10% reduction in body weight or a ≥25% improvement in the weekly average of daily hunger score at ~52 weeks of treatment.	Post Hoc Analysis
The proportion of patients aged ≥12 years who met categorical thresholds of 5%, 15%, 20%, 25%, 30%, 35% and 40% weight loss from baseline after ~52 weeks of treatment.	Pre-specified in study protocol
The proportion of patients aged ≥12 years who achieved a ≥10% reduction from baseline in body weight or a ≥15% reduction in BMI after ~52 weeks of treatment.	Pre-specified in study protocol
Change and percent change in BMI-z score from baseline after ~52 weeks of treatment in paediatric patients by age group (6-11 years and/or 6-16 years).	Post Hoc Analysis
Descriptive statistics for change and percent change from baseline in waist circumference after ~52 weeks of treatment	Pre-specified in study protocol
Descriptive statistics for change and percent change from baseline in total body mass (including body fat, non-bone lean mass and bone density) after ~52 weeks of treatment.	Pre-specified in study protocol

Summary statistics for global hunger response by active-treatment visit based on the questions: "Overall, how would you rate the hunger you experience now?" for patients aged ≥12 years; and "How hungry is your child acting now?" for patients aged <12 years.	Pre-specified in study protocol
Descriptive statistics for change and percent change from baseline in PWS-FPD and the Prader-Willi syndrome Sensory Experiences Questionnaire (PWS-SEQ) after ~14 weeks of treatment for cognitively impaired patients aged ≥12 years after ~52 weeks of treatment.	Pre-specified in study protocol
Descriptive statistics for change and percent change from baseline in measures of insulin sensitivity/resistance (fasting glucose, HbA1c, oral glucose tolerance test and insulin) after ~52 weeks of treatment.	Pre-specified in study protocol
Descriptive statistics for change and percent change from baseline in fasting lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides) after ~52 weeks of treatment.	Pre-specified in study protocol
SF-36 health survey version 2 (SF-36V2) and SF-10 health survey for children domain and composite summary score and change from baseline after ~52 weeks of treatment.	Pre-specified in study protocol
Quality of life after 14 and ~52 weeks of treatment, as measured by the Paediatric Quality of Life Inventory (PedsQL) or Impact of Weight on Quality of Life-Lite (IWQOL-Lite), age-dependent and EQ-5D actual scores and change from baseline.	Pre-specified in study protocol

Study stage at which exploratory endpoints were decided/ implemented in study RM-493-022

Exploratory endpoint	**At which stage of study was endpoint decided/ implemented?**
The proportion of patients with ≥10% weight loss.	Included to replace yearly mean percent change from baseline in body weight during study conduct.
Hunger, assessed at each visit using a daily questionnaire and 2 global questions.	Pre-specified in study protocol
Yearly body composition including total body weight loss, fat loss and non-bone lean mass.	Pre-specified in study protocol
Waist circumference, measured according to United States National Heart Lung and Blood Institute criteria.	Pre-specified in study protocol
Potential improvements in lipid levels (fasting cholesterol and triglycerides).	Pre-specified in study protocol
Quality of life was assessed yearly using the validated self-reporting instruments IWQOL-Lite (specific for obesity) for participants aged ≥18 years and the measurement model	IWQOL-Lite was pre-specified in study protocol.

Clarification Questions

for the PedsQL for participants aged <18 years. The validated self-reporting instruments SF-36 or SF-10 were used to measure functional health and well-being.	Use of SF-10 and PedsQL was included during study conduct, when the potential to recruit paediatric patients into the study was specified.
Biomarkers predictive of a setmelanotide response and/or rate of weight loss change could be evaluated using metabolic biomarkers. Such pharmacodynamic markers could include neuroendocrine and endocrine indicators of energy metabolism (e.g. ghrelin, leptin, insulin, orexin and oxytocin, peptide YY, glucagon-like peptide-1, melanocyte stimulating hormone, pro-insulin, adrenocorticotropic hormone, brain-derived neurotrophic factor) or anti-inflammatory markers such as high-sensitivity C reactive protein.	Pre-specified in study protocol
C-SSRS and PHQ-9 scores	Included during study conduct, when the potential to recruit paediatric patients into the study was specified.

Data/Results

A14. Priority Question: The CS states that "*only pivotal patient data were included in the primary endpoint at 52 weeks"* for RM-493-023. Please can you confirm if both pivotal and supplemental participants were included in the measurement of the following endpoints at 52 weeks:

a. BMI or BMI-z
b. Hyperphagia and hyperphagia related QoL
c. Obesity related QoL?

For all endpoints reported at 52 weeks, only pivotal patient data were included, incl. BMI and BMI-z, IWQoL and PedsQL. Hyperphagia and hyperphagia related QoL were not measured in the study.

A15. Priority question. Can you provide a plot of the mean change in BMI/BMI-z and/or weight over time for each treatment group, as you do in Fig 6 for hunger score? We would like to see this (i) for completers only and (ii) using imputation. There seems evidence of "regression to the mean" for the placebo group for hunger score. Is that the case for weight too? If so, this should be adjusted for.

Please see figures below for mean change in BMI and BMI-z over time for completers and mean change in weight using imputation, as requested. BMI, BMI-z and weight remained virtually unchanged for patients on placebo during the initial 14-week treatment phase, and hence would not require adjusting for. By comparison BMI, BMI-z and weight is reduced during the first 14 weeks of treatment.

After 14 weeks all patients are on setmelanotide, and patients initially randomised to placebo [redacted]. This is similar

to the effect that was already presented on the hunger score curve (figure 6 of the CS). In that figure, patients initially on placebo showed limited effect on hunger in the first 14 weeks, but then showed similar effect on hunger when transferred to setmelanotide than patients initially randomised to setmelanotide.

While we acknowledge that figure 6 of the CS appears to show a small initial placebo effect, we do not believe that it shows an apparent regression to the mean.

Mean Percentage Change in BMI (RM-493-023, Pivotal Patients With BBS)

Mean Percentage Change in BMI-z Score (RM-493-023, Pivotal Paediatric Patients With BBS)

Mean Percentage Change in Weight [Imputed] (RM-493-023, Pivotal Patients With BBS)

A16. The CS notes that some participants from the supplemental cohort for study RM-493-023 had not yet reached 52 weeks of follow up and their endpoint data was imputed using SAS, PROC MI (CS, pg 61). Please can you provide the baseline characteristics for participants whose follow-up data was imputed and for participants whose follow up data was not imputed.

Thank you for your request. However, we are unable to provide this data at this stage.

A17. What is the proportion of missing data for the 14 week outcomes in RM-493-023 trial by treatment arm? Did the imputation model allow for different reasons for missing in the 14 week data (drop-out) and the 52 week data (which occurs by design).

There are no missing data in the 14 weeks outcome in the RM-493-023 trial, regardless of the treatment arm. Only one patient discontinued therapy during the placebo-controlled period and that patient was randomised to placebo. The reason for discontinuation was adverse event (anaphylaxis) occurring while on placebo.

Thus, there is no answer to the question on the imputation model.

Clarification Questions

Section B: Clarification on cost-effectiveness data

Model Population

B1. Priority question. How will severity of hyperphagia be assessed in clinical practice and used to inform prescribing decisions of setmelanotide in BBS patients?

Setmelanotide will be initiated in one of the four existing specialist clinics for the management of BBS. Clinicians will base their decision to prescribe setmelanotide on the patient's weight trajectory, and on the extent to which eating behaviours are interfering with their ability to carry out their daily life.

When patients are obese and struggling with eating behaviours (as outlined in the description of severe hyperphagia presented below, which is taken from the vignette study carried out to determine the impact of hyperphagia on utility), they will be classified as having severe hyperphagia.

Clinical experts felt that the description below is reflective of their patients who are most severely affected by hyperphagia.

Severe hyperphagia description	
Subjective Experience	• You **almost never feel full** after a **normally sized meal** • You become **hungry again almost immediately** after eating a meal • Thinking about food **almost always interferes** with your **normal activities** of daily living
Observable Behaviors	• You overeat to the point of **discomfort at most meals** • You eat **almost constantly** • You eat during the **hour** before you go to bed **almost every night** • You **eat** a large number of calories when you wake up **during the night almost every night** • You try to **sneak food** without people knowing **almost every day**
Impact	• You become **extremely distressed or upset** when **denied food** • Because of hunger and eating behavior, you have **severe problems performing daily activities** such as self-care, getting around, leisure activities and work or school • Because of hunger and eating behavior, you have **severe problems with your relationships** with family and friends

B2. Priority question. What is the distribution of severity of hyperphagia in the obese BBS population in (i) children and (ii) adults?

Clinical experts have indicated that approximately 60% of children with BBS have severe hyperphagia using the description provided above. Experts also stated that while adult patients may mask their

hyperphagia symptoms better, their weight indicated that hyperphagia must still be an issue and so it was felt reasonable to assume that 60% of adults with BBS also have severe hyperphagia.

B3. Is contraception a requirement for taking setmelanotide? Would contraception drugs be offered to children, and would they effect weight/BMI?

Contraception is not a requirement for taking setmelanotide.

Morbid obesity is actually a risk factor for pregnancy, and in women with morbid obesity reducing BMI is advised when considering pregnancy.

However, for women who become pregnant while on setmelanotide, specific caution is advised to make sure that food intake is sufficient for the foetus to receive the nutrients required for proper development.

B4. Can you provide information on existing and new comorbidities in RM-493-023 and RM-493-022?

Patients who entered trials RM-493-023 and RM-493-022 experienced a wide range of comorbidities related to both:

- The presence and progression of Bardet Biedl Syndrome, such as retinal disease or blindness, renal failure, polydactyly, cognitive disorders, etc. and to
- The presence and progression of obesity such as Type II diabetes, hypertension, hyperlipidaemia, non-alcoholic fatty disease, asthma, sleep apnoea, etc.

The precise set of comorbidities and their severity varied for each patient.

It must be assumed that comorbidities related to the presence of Bardet Biedl Syndrome continued to develop and progress during the course of the study but this was not specifically monitored. There were no additional new and unexpected co-morbidities identified during the trials.

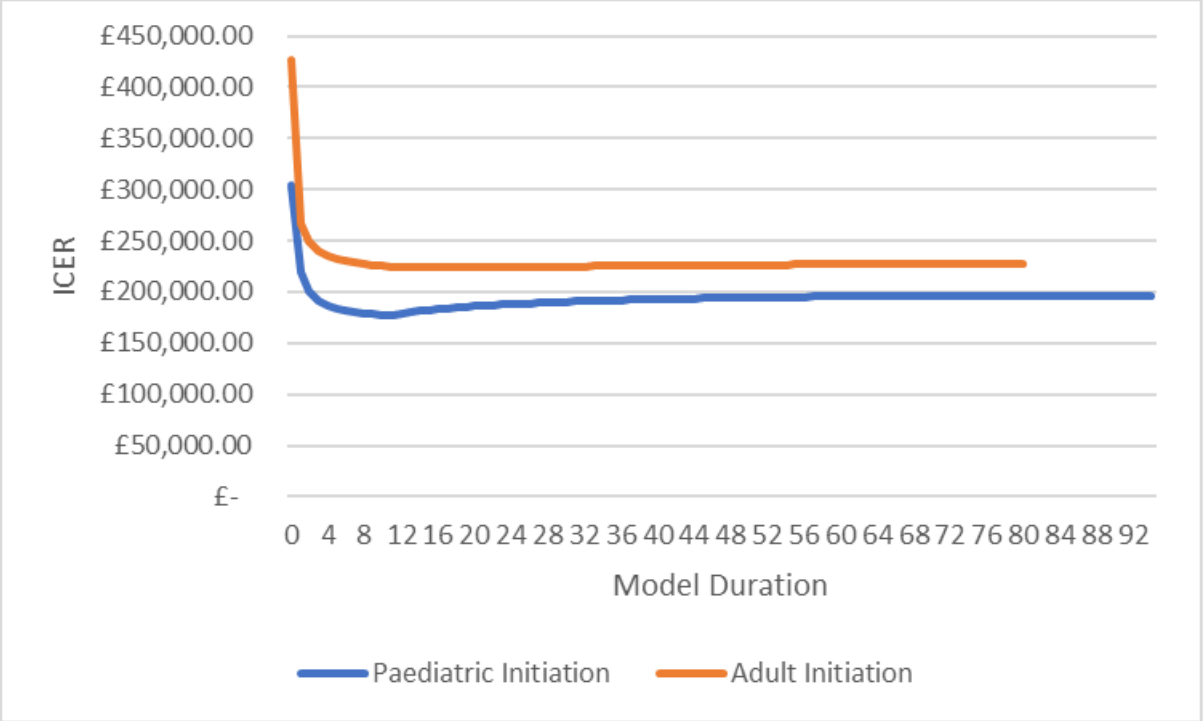
Model structure / code

B5. Priority question. The time horizon for this model is 100 years. Please provide scenarios to show the sensitivity of the results to shorter time horizons.

The NICE reference case is for an appropriate time horizon to capture the costs and benefits of treatment. Since setmelanotide is a treatment that continues for the lifetime of the patient and has mortality implications, we assumed a lifetime time-horizon for the model base case. However, since the model is evaluated in yearly periods, the time horizon can be evaluated yearly in terms of the accumulation of costs and health outcomes. The figure below displays the change in cumulative ICERs for both the paediatric initiated and adult initiated populations over various model time horizons, using the updated model results that reflect the alterations made in response to the clarification questions. We can see that the ICER is high for each population during the first year of treatment when the response status has yet to be confirmed and before the treatment effect on BMI/ BMI-z has

occurred. As the time horizon extends then the ICER falls for both populations, with the paediatric population experiencing a slight rise in the ICER as they move from the paediatric model to the adult model before levelling off.

ICERs for time horizons (model duration) up to 100 years



B6. **Priority question.** During time 0-11 of the model paediatric patients BM20:BM31 accrue negative QALYs, which lacks face-validity. We think this is due to applying additive utility decrements to the very low utility for severe hyperphagia. Can the company adjust the method for applying disutilities to avoid this?

Model timepoints showing negative QALYs in the paediatric model do not represent quality-of-life values below death for the patient. The accrual of negative utility is attributed to the caregiver utility decrement which is applied additively to the patient utility. For instance, if we were to alter the model to apply 0 disutility for caregiver burden in the current model, we can see that the accrued utility values for BSC at time 1 changes [redacted]

B7. Priority question. 'Cost & Clinical Outcomes'! During time 0 of the model patients who are non-responders are not accounted for in AD20:AJ20 and AD124:AJ124. 100% of patients are inW20:AC20 and W124:AC124 and able to accrue LYs in BL20, BL124, BN20, BN124 QALYs in BM20, BM124, BO20, BO124. So, how are the 86% proportion of patients that do not respond initially not accounted for in the model?

This point is taken, we had incorrectly applied the utility benefit of the hyperphagia treatment effect to the 100% of patients in year zero instead of to the 86% of responders – apologies for that oversight. The model has been adjusted such that non-responders (please note: 14% not 86%) do not receive the QALY benefit from hyperphagia in time 0 of the model, while responders are expected to experience the hyperphagia-related QALY benefit during the first year of treatment (year 0). Note that the treatment effect on BMI is assumed to not have an effect until the end of the first year of treatment and thus does not impact QALYs during time 0 of the model.

Apologies for any confusion relating to model time. This is a life table model and we had not considered how time 0 may be interpreted as a Markov model. In this model, time is added to the starting age. Thus, for a starting age of 6, row 20 is the first year of the model.

The impact of this adjustment, independently, increases the paediatric ICER from £191,759 to £193,656.

B8. 'Costs & Clinical Outcomes'! age is sometimes 18, other times 19, which is it?

The age is 18. After fixing this, the ICER increases slightly from the original value £191,759 to £192,572.

B9. 'Costs & Clinical Outcomes'!BJ20, BJ124 UndiscoutedTreatment costs multiplied by 14/15. What does that represent?

The multiplied value is 14/52, which reflects the length of time during which we expect non-responding patients to remain on treatment in year 1 of the model. Treatment response on hyperphagia is expected to be considered at 14 weeks, so non-responders will only experience 14 weeks of treatment costs as they are assumed to discontinue treatment at time of assessment.

Model clinical inputs

B10. Priority question. The model assumes a survival benefit (SMR=0.85) due to non-obesity related causes. Please justify why Setmelanotide would be expected to reduce mortality other than via obesity and obesity-related complications, when the treatment only acts on hunger and BMI/BMIz. Where does the value of 0.85 come from?

There is evidence that hyperphagia is associated with causes of mortality that are independently of obesity, e.g. choking, gastric rupture and/or respiratory illness[2].

Clarification Questions

Thus, the SMR value of 0.85 was an assumption based on the level of impact we would expect setmelanotide to have on this hyperphagia related mortality.

That said, the mortality treatment effect has limited impact on model outcomes. In the base case, removing the setmelanotide SMR for responding patients (setting the value to 1) changes the ICER from £191,759 to £191,596.

Given that we are unable to precisely quantify the impact of setmelanotide on hyperphagia related mortality at this stage, we have set the SMR to 1 in the revised version of the model.

B11. Priority question. Please give a justification why the Setmelanotide effect would not wane over time. For example the effect of other treatments for obesity (eg GLP-1's) have been shown to wane over time (the TEEN studies). Is there any reason to expect the waning of Setmelanotide to be different from GLP-1's?

The model assumes that all patients who do not show a significant response on hyperphagia in the first 14 weeks of treatment associated to initiation of weight loss, will not continue on treatment. Those who respond to treatment in terms of hyperphagia reduction go on to show a reduction of their weight trajectory and are considered responders to setmelanotide.

Setmelanotide's mechanism of action is to replace the missing activation of the MC4R receptor, the impact of which is to reduce hyperphagia and thereby facilitate weight loss as patients no longer suffer insatiable hunger. There is no reason to believe that patients who respond to setmelanotide initially will not continue to do so. It is therefore assumed that there would not be any waning of treatment effect on hyperphagia. However, if patients and their treating physicians were to see a waning of the treatment effect of setmelanotide, that is a return of their hyperphagia, then it is reasonable to assume that treatment would be discontinued at that time. Thus, the impact of treatment waning can be proxied by the discontinuation parameter that is already included in the model.

B12. Priority question. The model assumes treatment effect of a reduction in BMI / BMI-z of 2 levels for paediatric responders and 1 level for adult responders. However, mean change in BMI-z for paediatric patients (n=9) of -0.7 (Forsythe et al 2021) seems to correspond to 1 class change in BMI-z categories rather than 2 class change modelled. Mean change in BMI of adult patients at 52 weeks (n=11) -9.4% (Forsythe et al 2021) would lead to 1 class change in adults with higher BMI but not necessarily for adults with lower BMI example < 30 kgm^2. From the CS Tables 34 and 35 [redacted] Why not use assumptions that are in line with the results on the continuous scale?

As shown in table 34, all adult responders showed a reduction in obesity of at least [redacted], except for one patient who showed a reduction of [redacted]. We thus used as an assumption for the model a reduction of [redacted]. In patients with lower BMI (for example < 30 kg/m^2), overweight is

defined as 25-30 kg/m^2 and normal weight as 18.5-25 kg/m^2. It is thus possible that patients with normal weight lose about 5 points of body weight without changing obesity category but that would only happen if they were classified as normal weight. These patients would not be considered candidate for therapy as they would not be obese and are thus not part of the target indication nor part of the model.

In the paediatric population, efficacy appears more variable in table 35 than for the adults. However, it should be noted that [redacted] classified as "not changing level" have an extremely high starting BMI-z (4+), significantly above that of the upper limit chosen in the model that was based on availability of data to estimate the risk of comorbidities and in the disutility of obesity.

These [redacted] patients show a clinically significant (>0.2 points) reduction in BMI-z. Such patients are not formally changing class in table 35 but the clinically significant reduction in BMI-z translates in real-life in a strong reduction in the risk of comorbidities and in the disutility of obesity.

[redacted] showing a decrease [redacted] actually lost [redacted] in BMI-z. and [redacted] now clearly not obese. The reason why [redacted] not decreasing more than one level is due to the fact that below BMI-z of 2, changes in class requires a 1-point reduction in BMI-z.

As a result, we believe that the paediatric data show consistency of reduction in BMI-z and consistency in clinical benefits for the patients and that using a reduction of [redacted] on average is a fair representation of change in that population and a valid hypothesis for the model.

B13. What criteria would be used to stop using Setmelanotide in clinical practice?

In clinical practice treatment with setmelanotide would be stopped if patients reported that their hyperphagia was no longer being controlled, and if, as a consequence they were regaining weight.

Input from the expert patient during the committee meeting for HST21 illustrates how missing a dose of setmelanotide leads to rapid reoccurrence of hyperphagia, felt by the patient as extreme hunger and craving for food. It would follow that it would also become rapidly apparent to the patient if setmelanotide was no longer controlling their hyperphagia.

In case of weight regain despite maintained control of hyperphagia, it would be important for the treating physician to identify if there is any other reason responsible weight regain. This could include:

- Natural reasons such as puberty
- Clinical reasons such as progression of co-morbidities or change in resting energy expenditure.
- Initiation of other therapies leading to weight gain (e.g, corticosteroids)
- Change in patient diet or discontinuation of exercise program (for example due to progression of retinal disease)

In such a situation the clinician will need to evaluate if the benefit of setmelanotide on hyperphagia and on preventing even greater weight gain justifies continuation of therapy

Costs

B14. Unit costs used to value resource use should be updated to reflect the most up to date costs available (i.e., the 2022 unit costs for health and social care and the 20/21 national cost collection data). Can you update these in the model please.

Unit costs have been updated to the most recent data available.[8,9] Complete blood count, liver function test and comprehensive metabolic panel costs now reflect 2023 private test prices. These updates have no impact on model outcomes as setmelanotide patients are not expected to experience any additional testing compared to BSC patients. The cost of a physician visit has been updated to now reflect the 2023 PSSRU publication describing the cost of a general practitioner visit. Updating these values changes the previous ICER from £191,759 to £191,771.

B15. Priority question: Please justify why the setmelanotide group has lower monitoring costs compared with the placebo group (CS Table 67). We heard that patients prescribed Setmelanotide would likely be managed in secondary/tertiary care and require active monitoring and treatment of adverse events in secondary/tertiary care as well. If so, where in the model have these costs been accounted for?

We accept the EAG's feedback on this point. We envisage the following monitoring for the setmelanotide group:

- Initial Face to Face appointment to initiate treatment
- Periodic telephone appointments until maintenance dose is achieved
- Face to Face appointments at Months 3, 6, 9 and 12, on treatment
- Then after a year on treatment, patients will visit the BBS service with frequency similar to current regular patient reviews, most likely once a year

Therefore, we expect setmelanotide patients to experience 3 additional physician visits compared to BSC patients in year 1. In the remaining years on treatment, we expect a reduction in physician visits to 1 per year. This update alters the ICER from £191,759 to £191,769.

B16. In table 16, you give discontinuation rates, but can you provide the breakdown of these by treatment at 14 weeks and 14- 52 weeks? Were the discontinuations reported for placebo including discontinuation after switching to setmelanotide?

One patient discontinued during the initial 14 weeks placebo-controlled phase. That patient initially was assigned to the placebo group and the reason for discontinuation was anaphylactic reaction.

The other [redacted] who discontinued did so between week 14 and 52.

[redacted] patients initially assigned to setmelanotide

[redacted]

Clarification Questions

[redacted]

[redacted] patients initially assigned to placebo and who withdrew after switching to setmelanotide the causes were:

[redacted]

The adverse events experienced by patients either lead to discontinuation, or were mild and transitory, resolving during the titration period.

B17. As per B14 can you provide adverse events by treatment at 14 weeks and 14-52 weeks. Are the adverse events reported for the placebo group including those after switching to setmelanotide? If so can you provide these prior to switching.

We do not have the details of the adverse events during the two periods for the BBS only population.

However please find below the Overview of Treatment emergent adverse events overall by treatment group for the full study (including AS patients), in the double-blind placebo controlled period and for the full trial duration.

Patients with at least 1:	**Double-Blind Placebo-Controlled Period**			**Full Study**		
	Setmelanotide (N = 27) n (%)	**Placebo (N = 25) n (%)**	**Total (N = 52) n (%)**	**Setmelanotide →Setmelanotide (N = 27) n (%)**	**Placebo →Setmelanotide (N = 25) n (%)**	**Total (N = 52) n (%)**
TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-Emergent Related Adverse Event[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious Related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE Leading to Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE Leading to Study Drug Withdrawal[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE Leading to Study Drug Withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utilities

B18. Priority question. Can we have mapped PedsQL utility values OR EQ-5D utilities and VAS scores (respectively) from the RM-493-023 trial patients be reported for responders and non-responders separately in the first 14 weeks of the trial and the 52 weeks of the trial for (i) children and (ii) adults? What is the correlation with weight-loss / BMI reduction?

Although PedsQL data was collected during in the trial; the dataset was too small to allow mapping of PedsQL or EQ-5D and VAS scores. Similarly, data do not allow for a separate analysis at 14 weeks and 52 weeks.

In adult patients (n = 11), statistically significant correlations were observed between percent change in IWQOL-Lite and percent change in body weight (Spearman correlation coefficient, − 0.79; P = 0.0037) and BMI (− 0.74; P = 0.0098)[3].

No significant correlations were observed between change in body weight or BMI-z score and PedsQL score. However, correlations in the paediatric population were difficult to assess given the limited sample size[3].

B19. Priority question. All patients using setmelanotide reported side effects and adverse events, of varying degrees of severity, which would affect their quality of life. These are not picked up in the disutilities derived from the vignette study. Please include disutilities for adverse events and side effects related to using setmelanotide.

The main side-effects experienced by patients taking setmelanotide during study RM-493-023 were skin hyperpigmentation [redacted], injection site erythema [redacted], nausea [redacted] and vomiting [redacted]. Nausea and vomiting, in patients remaining on treatment were mild and transitory, resolving during the titration period. Reports from KOLs involved in previous setmelanotide clinical studies are that the impact of skin hyperpigmentation on utility is highly variable; for some patients, especially those with pale skin it can be welcome, for others with darker skin it may be less welcome. Assigning a population-based utility value to skin hyperpigmentation is therefore not deemed appropriate.

Disutilities associated with treatment-related adverse events have been added to the updated version of the model. As we expect these adverse events to resolve during the treatment titration period, the disutilities are applied for 2 weeks during the first year of the model. Applying a 0.04 disutility[4] to [redacted] of the population for nausea and vomiting and a 0.011 disutility[5] to [redacted] of the population for injection site erythema changes the ICER from £191,759 to £191,797.

B20. The company cites the precedent of using the vignette study in HST 21. In HST 21, alternatives to the use of the vignette study were utilities derived from the SF36 questionnaire, which were not generally validated for children. Please justify the use of the vignette study to inform disutility of hyperphagia in the context of this submission, where other options are available (EQ-5D for adults, and mapped utilities from the PedsQL for children).

The vignette study was deemed to provide the most accurate data on the impact of hyperphagia on quality of life. The Vignette study was a rigorous study carried out in 215 members of the UK general population using a time-trade-off (TTO) approach as described in TSD11 'Alternatives to EQ-5D for generating health state utility values'.[6] The definition of the vignettes for mild, moderate and severe hyperphagia were based on symptoms detailed in the Second Consensus Conference on Hyperphagia.[10] These definitions were then further validated through discussions with clinicians experienced in treating patients with hyperphagia in the UK and in the US. The Vignette study is therefore the only published data source for hyperphagia utility values and as such is the most credible evidence available on which to base utility values for mild, moderate and severe hyperphagia.

Whilst EQ-5D data were collected during the trial, it was felt that EQ-5D was not sensitive enough to capture the impact of hyperphagia on quality of life due to the lack of conceptual overlap between the five quality of life domains of the EQ-5D and hyperphagia. The quality-of-life values reported in study RM-493-023 indicate that patients with BBS have a quality of life slightly below population norms, which seems at odds with a disease whose manifestations can include obesity, hyperphagia, vision loss, undeveloped genitals and kidney failure. It is therefore apparent that these quality-of-life scores do not accurately reflect the lived experience of BBS patients. It has previously been suggested that EQ-5D does not fully capture the impact of sensory impairment on quality of life[7] and we would suggest that the same is true for hyperphagia.

In terms of the PedsQL data that was collected during the trial; the dataset was too small to allow mapping to EQ-5D. In any case, mapping would not solve the problem of lack of sensitivity of EQ-5D to hyperphagia.

B21. The utility multiplier reported in Table 74 applied for hyperphagia is markedly higher for moderate to severe, than mild to moderate. Please justify this large effect.

Mild	0.91
Moderate	0.70
Severe	[redacted]

The main difference between moderate and severe hyperphagia is the significant disruption to daily life caused by the all-consuming nature of severe hyperphagia. Severe hyperphagia results in patients almost never feeling full after a normal sized meal and becoming hungry again almost immediately, eating to the point of discomfort. The pre-occupation with food has an impact on work, school and relationships. Whilst moderate hyperphagia still involves lack of satiety and over-eating, it does not fall under the category of 'all-consuming'. Hyperphagia severity does not follow a linear progression.

Clarification Questions

B22. Updated Cost-Effectiveness Results

Based on the EAG feedback, we have updated the model with the following alterations in response to the listed clarification questions:

- Setmelanotide non-responders (14%) do not receive the QALY benefit from hyperphagia in time 0 of the model, while responders (86%) experience the hyperphagia-related QALY benefit during the first year of treatment (year 0).
- Corrected Cost and Clinical Outcomes equations to switch to BMI from BMI-z at age 18.
- Eliminated the setmelanotide treatment effect on mortality by setting this SMR parameter to 1.
- Unit costs updated to reflect the most recent available data.
- Adjusted setmelanotide monitoring costs to reflect 4 physician visits in year 1, compared to one visit for BSC patients.
- Incorporated disutilities for nausea/vomiting and injection site erythema for setmelanotide patients during the first 2 weeks of treatment.

The updated base case model results are provided in the table below.

Technologies	Total costs (£)	Total LYG	Total QALYs	Total Undisc. QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental undisc. QALYs	ICER incremental (£/QALY)
BSC	£117,310	24.12	0.93	2.90					
Setmelanotide	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	Commercial in confidence data removed	£194,495

Section C: Textual clarification and additional points

Missing Information

C1. The CS states *"In patients assessed as cognitively impaired, hunger was assessed using the Prader-Willi syndrome Food Problem Diary (PWSFPD), a caregiver-completed questionnaire designed to assess behaviours associated with hunger".* Please provide a reference for the Prader-Willi syndrome Food Problem Diary. The CS states *"In patients assessed as cognitively impaired, hunger was assessed using the Prader-Willi syndrome Food Problem Diary (PWSFPD), a caregiver-completed questionnaire designed to assess behaviours associated with hunger".* Please provide a reference for the Prader-Willi syndrome Food Problem Diary.

The PWSFPD was developed by Rhythm researchers to assess food-related behaviours among patients that experience hyperphagia. It was used initially in a Prader-Willi trial whose results were negative so no publication followed. The clinical team decided to include the same questions in the follow-on BBS trial for cognitively impaired patients but we cannot provide a reference for it.

C2. Please could you provide the protocols for the three reviews that you report in the submission? Namely protocols for the reviews of Clinical effectiveness, Cost effectiveness, and HRQoL.

Please find protocols provided separately.

Differences between documents

C3. Please can you confirm which table of patient characteristics is correct for the RM-493-023 study? Table 12 of CS has different ethnicity numbers for each group, compared to Supplementary Table 4 published in the appendices of the Lancet Diabetes and Endocrinology publication of the study {Haqq, 2022 #18}.

The Haqq supplementary table contains the accurate data. There was a line inversion in table 12 between Hispanic and Latino and Non-Hispanic and Non-Latino. We apologise for the mistake.

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6. Brazier J, Rowen D. NICE Decision Support Unit Technical Support Documents. In: *NICE DSU Technical Support Document 11: Alternatives to EQ-5D for Generating Health State Utility Values.* London: National Institute for Health and Care Excellence (NICE); 2011

7. Perneger TV, Courvoisier DS. Exploration of health dimensions to be included in multi-attribute health-utility assessment. *Int J Qual Health Care.* 2011;23(1):52-59

8. DocTap. Blood test prices. https://doctap.co.uk/blood-test/cost. Published 2023. Accessed 27 Feb 2023.

9. Jones KWH, Birch S, Castelli A, et al. Unit Costs of Health and Social Care 2022 Manual. In:2023.

10. Heymsfield SB, Avena NM, Baier L, et al. Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia. *Obesity (Silver Spring)*. 2014;22 Suppl 1(0 1):S1-s17.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Bardet-Biedl Syndrome UK (BBS UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	BBS UK is the only UK registered charity supporting people with Bardet-Biedl syndrome (BBS), their families and carers. We are a user-led organisation, managed by a board of trustees, the majority of whom have lived experience of the Syndrome. The Charity has a contract with NHS England to provide support, facilitation and advocacy services to specialised multi-disciplinary clinics that are held in London and Birmingham. This enables us to directly influence the quality of care for those with BBS and to improve the understanding of this complex condition among medical professionals. Listening to and sharing our community's experiences has enabled us to become experts in our own condition, and strengthens our knowledge and the support that we can give to each other. We have 640 individuals diagnosed with BBS on our database and appx 950 members, including parents/carers, extended family members and professionals. In addition to our clinics support service (funded by NHS England), we provide an Advice Service, annual weekend conference, information booklets and regular newsletters, funded by grant applications and community fundraising.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	Rhythm Pharmaceuticals provided £7,000 sponsorship to the BBS UK conference to contribute towards the running costs of the meeting. Our annual family conference weekend brings our community together with interested professionals and experts, to learn about the latest developments, treatments and research in BBS and to participate in tailored workshops. The wellbeing that comes from meeting others living with the same condition and facing similar challenges is immeasurable. Rhythm had no influence over the creation, development or content of the meeting.

the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	BBS UK conducted an anonymous Obesity Impact Questionnaire with our community, from September 2022 to December 2022, to capture their experiences of hyperphagia and obesity for this submission; although the response was limited (appx 20 participants), the information shared with us was invaluable and consistent with our wider understanding and individual experiences of BBS and the associated hyperphagia and obesity. Some quantitative data was taken from a BBS UK membership audit, conducted from February 2021 to June 2021 (40 respondents). We have also drawn on the experiences shared with us by our members anecdotally, our own lived experience of the syndrome, and through our work as patient liaison officers within the BBS clinics service. Finally, we have incorporated the personal perspective of 'Louise', via a written document and supplemented by answers to questions via email. Louise took part in a clinical trial for the treatment under review and wished to contribute to the appraisal process whilst also protecting her privacy.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Bardet-Biedl syndrome is a multi-system complex disorder featuring severe visual impairment and obesity among many other symptoms. Sight loss begins in childhood and registration of blindness typically occurs in the mid-teens. In our Membership Audit (2021), 88% told us that BBS had a moderate, severe or very severe impact on their life/their child's life. In our recent Obesity Impact Questionnaire (2022), 88% of respondents reported experiencing hyperphagia. Hyperphagia is present from babyhood which is extremely distressing for the child and their parents. Obesity can set in very early as parent/carers respond to their hungry child's needs. Children, young people and young adults with BBS are reported to have taken food out of bins, hoarded food for later eating, eaten whatever foods are to hand in large quantities, including, for example, ketchup and butter. Parents report keeping cupboards

	locked and having to monitor their child at all times when around food. Parents and carers face an endless battle over food which is exacerbated by the emotional immaturity of BBS. This goes on into young adulthood and beyond and significantly impacts on the wider family, especially siblings. In our Membership Audit, 78% told us that having BBS impacts on their family life and 87% said that it impacts on their relationships with family and friends. The emotional and communication difficulties, anxiety, low mood and depression that are present in BBS together with hyperphagia have a profound impact on the patient's wellbeing and quality of life. The resulting obesity further impacts on anxiety, low mood, depression and self- esteem. In our Membership Audit, we asked about the emotional and psychological impact of having BBS (as a whole), respondents reported experiencing: • Anxiety: 78% • Loss of confidence: 63% • Stress: 58% • Fear: 53% • Anger: 45% Hyperphagia and obesity significantly impacts on the quality of life of those affected. In our Obesity Impact Questionnaire, we asked our community how living with hyperphagia makes them feel, they said: • I feel [hungry] all the time and it never goes away. • I want to snack and feel full, [it] makes me feel bad. • Food is in my thoughts all day and I snack between meals. • My child is constantly hungry and never satisfied. • She is constantly hungry, once eaten, she will sign that she is still hungry no matter what she just ate. • My son feels the need to eat a lot of time, even after just having breakfast or lunch or dinner, wanting more food most of the time. • Angry when hungry or becomes aggressive if food is denied. • She has regular meltdowns due to not getting food when she wants it and/or not quickly enough. • It's difficult because she is constantly seeking food and when you say no there is normally a meltdown.

We asked them to tell us about how obesity impacts on their day-to-day life, they said:

- Tired, emotional, depressed and stops me doing the things I want to do.
- Lack of motivation, sleep problems, low self-esteem, general aches and pains daily
- It affects me emotionally, my mobility and my general wellbeing.
- I am constantly watching her to make sure she isn't taking more food. I have to constantly plan what the next meal is. I am always reading food labels. I find food to be the biggest argument we have in our house, also the most frequent.
- It has a massive impact on her daily life. It affects her sleep and concentration, particularly in school. Her weight gain is continuous and is putting immense pressure physically on her body.
- Obesity is putting a massive strain on her mobility. She is in constant pain, particularly around her knees and ankles. She has to use a wheelchair when out and about.
- It affects both their physical and mental health. Obesity makes exercise a challenge and they don't feel good enough or confident enough to participate, which has a knock on effect with low self-esteem and lack of confidence.
- We are extremely worried about our child's obesity and it causes constant stress and worry. We try to limit her intake of calories but find it extremely hard to manage.

Louise's story: "I was born a small healthy baby. From birth, I was a hungry baby, even after being fed. From nursery and throughout school age, I was considerably larger than my peers. I hid food, so it was readily available when required. From secondary school onwards, I had very wide feet, and had to wear boys' shoes. The impact on being large, caused problems with school uniform, again having to wear boys clothing. This made me feel very conscious of size, and sometimes caused bullying. Moving onto late teens and adulthood, it was difficult to find nice clothing, having to shop at outsize retailers. This affected my self-esteem, and confidence. **I** tried a number of diets without success. Weight fluctuated up and down, but never stayed off. Hunger pangs were constant, and if not addressed, made me feel sick, forcing me to eat. Very shortly after eating, I was already thinking about the next meal."

7. What do patients or carers think of current treatments and care available on the NHS?	There is a lack of understanding about the hyperphagia in BBS and about BBS in general at a local level. Accessing local dietetic support is an ongoing challenge and where this is offered, the lack of understanding often leads to loss of trust and a breakdown in communication. There are currently no other treatments available for hyperphagia and BBS patients often do not meet wider criteria for other weight-loss treatments. Specialised treatments and associated support are needed. BBS patients have access to excellent specialised dietetic support within the multidisciplinary BBS clinics, however appointments are every 18-24 months and take place in two centralised locations, London and Birmingham. Those who completed our questionnaire spoke about the following treatments/care: • Bariatric surgery/gastric band – three respondents reported considering this option but decided it wasn't for them, because although surgery restricts food intake but doesn't address the hunger. • Metformin – 'was helpful for a while'. • Methylphenidate – we are aware that some BBS patients are taking this for the appetite suppression element as well as for ADD. • Respondents reported that the BBS clinics dietitians were supportive, however they had been unable to access local dietetic support. **Louise's experience of current NHS treatments and care**: "I took many trips to the doctors over the years, concerned about weight and doctors did not know the full effects of BBS and did not get the complexity of the condition. I was constantly offered medication for blood pressure, cholesterol and sugar control before looking into the effects of BBS; I have never been offered weight loss drugs on the NHS. I was referred to dietitians on many occasions, and given information regarding bariatric surgery. Even after my BBS diagnosis the local dietician support was very hit and miss and trying to get them to understand the severe hunger aspect has been very difficult. I felt like judgement was always there and that no matter how hard I would try, weight loss could not be maintained and seeing a dietician every week made me feel like I was being judged and I felt a failure; as you can imagine self-esteem and confidence was not good.

	I attended a six week course run by the NHS to help manage food, weight and sugar level controls; the tutors of the course had never had anybody with a sight impairment and all materials were in hardcopies meaning I could not participate in the course independently and had to keep getting information read out which made me feel embarrassed and that I was a burden even though it wasn't my fault.
8. Is there an unmet need for patients with this condition?	Listening to and understanding the lived experience of our community, we are of the opinion that yes, there is an unmet need for patients with BBS; current treatments on offer do not address hyperphagia which significantly impacts on the wellbeing and quality of life of those affected.

9. What do patients or carers think are the advantages of the technology?	Since the first results from the trials in the US were released, our community have been showing a keen interest and asking when they will have access to Setmelanotide – they are hopeful because they understand that it specifically targets hyperphagia which will give them the support they need to lose weight. We asked our community to give their thoughts about the advantages of Setmelanotide, they told us: • Weight loss – feeling proactive about my condition. • It would help with the constant hunger feeling. • Help people who are constantly hungry to not feel that frustration, stress and anxiety is an incredible advantage. In all honesty I think the weight loss would be considered more as an additional benefit • I believe the advantages are the reduction in feeling hungry all the time. **Louise took part in the Setmelanotide trial** in the UK, she said: "Fairly soon into the trial, it was obvious I was losing weight, inches off the body, and hunger pangs had disappeared. At the end of the trial, I lost 10% of body weight, with a significant reduction in cholesterol, liver function, blood pressure and sugar levels. After losing weight, I felt healthy and was enjoying the reduction in clothing size. I received many compliments from friends and family, and my self-esteem and confidence had grown immensely. Once the trial ended, the hunger pangs returned and the amount of food eaten was raised, along with weight, inches and clothing size. Emotions and self-esteem have been affected. Recent blood tests have confirmed the rising of cholesterol, liver function, blood pressure and sugar levels. If Setmelanotide was offered to me, I wouldn't hesitate to accept it."

10. What do patients or carers think are the disadvantages of the technology?	A minority felt there weren't any disadvantages however common concerns focused on the injection, both in terms of disliking needles, but also around how they would manage the treatment due to their sight impairment. Support would be needed which was a particular disadvantage for those who are living independently. Carers concerns focused on having to administer the injection, the potential side effects (skin colour changes) and that it potentially requires lifelong use.

Disadvantages of the technology

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Those who have BBS are visually impaired and may also have poor co-ordination and/or reduced fine motor skills. Support will therefore be needed to administer this treatment, which may put some at a disadvantage, for example those who live independently, or whose carer is not willing or able to administer the treatment for them.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• BBS and the associated hyperphagia and obesity significantly impacts on the quality of life of those affected including their parents, carers and siblings. • There is currently no alternative treatment available to address hyperphagia in BBS. • Standard weight loss treatments are ineffective in those who experience hyperphagia. • The method of administration is not accessible for BBS patients due to sight loss and other symptoms which may lead to inequity of access – attention must be given to this •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] on behalf of the British Obesity and Metabolic Surgery Society
2. Name of organisation	British Obesity and Metabolic Surgery Society (BOMSS)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	BOMSS is a society of surgeons and other health professionals (physicians, nurses, dieticians, psychologists and GPs) who specialise in the treatment of severe obesity and its metabolic complications. Our mission is to promote the highest standards of expert multidisciplinary care for those living with complex obesity through delivery of education, training opportunities, research and through the promotion of cohesive team working in high quality bariatric surgery centres. We are the UK's internationally recognised bariatric surgery society and provide expert advice to a variety of bodies to inform national policy and commissioning guidance promoting the safe and equitable practice of obesity surgery. Funded by membership fees and industry partners.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BOMSS organises an Annual Scientific Meeting in which industry partners acts as sponsors contributing to the cost of the meeting. The list of sponsors changes every year but includes manufacturers in the field of obesity (pharmacotherapy, lifestyle interventions and endoscopic treatment options) and obesity surgery (manufacturers of equipment used in bariatric surgery). Furthermore, BOMSS have sponsors supporting activities again from the same list of manufacturers.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Weight loss maintenance improving health, function and quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	10% weight loss.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Effective obesity treatment options are needed for obesity and particularly Bardet-Biedl Syndrome.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With lifestyle intervention and occasionally bariatric surgery.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The guidelines for obesity treatment in children, young people and adults.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined for all age groups.
9c. What impact would the technology have on the current pathway of care?	It will be delivered as part of multi-disciplinary care in specialised units.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used as part of current practice in obesity management services.
10a. How does healthcare resource use differ between the technology and current care?	The cost of the treatment (setmelanotide) will need to be balanced with the outcome (improvement in obesity, obesity associated disease and quality of life). There is likely to be a reduction in cost to the NHS for patients who respond well to the treatment.
10b. In what clinical setting should the technology be used? (For example,	Specialist obesity clinics, adult or paediatric.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The small population who will be treated due to the low prevalence of the Bardet-Biedl Syndrome means that the investment needed will be low. Treatment will be provided in the already available clinical settings.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In an RCT, 32.3% of patients aged 12 years or older with Bardet-Biedl syndrome reached at least a 10% reduction in bodyweight after 52 weeks of setmelanotide. This is clinically important. The advantage compared to bariatric surgery is the avoidance of surgery. The effect of bariatric surgery in patients with Bardet-Bield syndrome is variable and may be less in comparison with other patients with severe obesity. Haqq AM Chung WK Dollfus H et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period.Lancet Diabetes Endocrinol. 2022 Dec;10(12):859-868. Gantz MG, Driscoll DJ, Miller JL et al. Critical review of bariatric surgical outcomes in patients with Prader-Willi syndrome and other hyperphagic disorders. Obesity (Silver Spring). 2022 May;30(5):973-981.
11a. Do you expect the technology to increase length of life more than current care?	Weight loss maintenance of this magnitude is likely to lead to improved survival acknowledging that this has not been tested for setmelanotide yet.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Weight loss maintenance of this magnitude is likely to lead to improved quality of life
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/A

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Compared to bariatric surgery, setmelanotide would be more acceptable to patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clearly an accurate diagnosis of Bardet-Biedl will be needed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The benefits of weight loss are likely to be captured by the QALY calculation.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This technology assessed galvanises the use of targeted therapy in people living with obesity after accurate assessment, diagnosis and precise staging of the disease including the use of genetic diagnostics. The benefit of weight loss will be impactful in obesity and obesity associated disease.
16a. Is the technology a 'step-change' in the management of the condition?	Providing effective and safe obesity care in another group of individuals with a monogenic cause of obesity is important and a step in the right direction. As setmelanotide is already approved for treating obesity caused by LEPR or POMC deficiency, this is an incremental, but important development.
16b. Does the use of the technology address any particular unmet need of the patient population?	The need for effective and safe obesity care remains largely unmet. Setmelanotide for treating Bardet-Biedl syndrome addresses a small number of people for whom currently available treatment provide a variable effect.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Major side effects are uncommon and they are likely to affect the tolerability of the treatment rather than the disease itself.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The randomised clinical trial incdlued patients in the UK as well as USA, Canada, France, and Spain. Haqq AM Chung WK Dollfus H et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period.Lancet Diabetes Endocrinol. 2022 Dec;10(12):859-868.

18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Weight loss maintenance, effect on obesity associated disease and quality of life.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Skin tanning and occasionally hair colour darkening has been reported in patients receiving setmelanotide.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE HST guidance [HSTXXX]?	No.
21. How do data on real-world experience compare with the trial data?	The real world data are not available yet but are likely to reflect the trial data as the clinical setting and the treated population are likely to be similar.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Obesity stigma is well documented and rife. Access to effective care for people living with obesity should be prioritised.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Setmelanotide is safe and effective in the short term for patients with Bardet-Biedl Syndrome • The only comparative treatment in terms of effect, bariatric surgery, has a variable effect and requires a surgical procedure. • There is an unmet need for effective treatment modalities for obesity. • The relatively small number of people with Bardet-Biedl syndrome will benefit from a novel treatment option. • The treatment can be provided in currently available infrastructure.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Obesity and hyperphagia (Bardet-Biedl syndrome) - setmelanotide

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation

Produced by: Bristol Technology Assessment Group, University of Bristol

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Jelena Savovic, Rachel James, Chris Cooper, and Deborah Caldwell summarised and critiqued the clinical effectiveness data reported within the company's submission. Ayman Sadek, Elsa Marques, Joe Carroll, and Nicky Welton critiqued the health economic analysis submitted by the company. Nicky Welton critiqued the statistical aspects of the submission. Chris Cooper critiqued the company's search strategy. Professor Julian Hamilton-Shield and Dr Lukas Foggensteiner provided clinical advice. All authors were involved in drafting and commenting on the final report.

[redacted]

[redacted]

Abbreviations

Abbreviation	Definition
AEs	Adverse Events
AS	Alström syndrome
ATB	Active Treatment Baseline
BBS	Bardet-Biedl syndrome
BMI	Body Mass Index
BMI-Z	Body Mass Index Z score
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CS	Company Submission
EAG	Evidence Assessment Group
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 dimensions
EQ-5D-3L	EuroQol 5 dimensions 3 level
EQ-5D-5L	EuroQol 5 dimensions 5 level
ERG	Evidence Review Group
FAS	Full Analysis Set (as defined in company submission)
GLM	Generalised Linear Model
GLP-1	glucagon-like peptide-1
GPs	General Practitioners
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
IWQOL lite	Impact of Weight on Quality of Life-Lite
LEPR	leptin receptor
MC4R	Melanocortin 4 receptor
MI	Myocardial infarction
MRR	mortality rate ratio
NA	Not Applicable or Not Assessed (depending on context)
NAFLD	non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHS EED	National Health Service Economic Evaluation Database
NI	No information (used in risk of bias tables only)
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research

NR	Not Reported
PCAS	Placebo-Controlled Analysis Set
PCPB	Placebo-Controlled Period Baseline
PedsQL	Paediatric Quality of Life Inventory
PICOS	Population, Interventions, Comparators, Outcomes, Setting
PN	Probably No
POMC	Proopiomelanocortin
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PWS-FPD	Prader Willi Syndrome Food Problem Diary
PY	Probably Yes
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RGDO	Rare Genetic Disease of Obesity
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SD	Standard Deviation
SE	Standard Error
SLR	Systematic Literature Review
SMR	Standardised Mortality Rate
TAG	Technology Assessment Group
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischaemic Attack
TTO	Time-Trade-Off
VAS	Visual Analogue Scale

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

- Section 1.1 provides an overview of the key issues.
- Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER
- Sections 1.3 to 1.6 explain the key issues in more detail.

Background information on the condition, technology and evidence and information on non-key issues are provided in the main body of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 provides an overview of the EAG's key issues:

Table 1 Summary of key issues

ID3947	Summary of issue	Report sections
Key Issue 1	In the absence of a validated measure of hyperphagia, how will BBS patients with severe hyperphagia be identified in clinical practice?	Sections 2.2, 4.2.3, and 6.1
Key Issue 2	Are the findings of studies RM-493-023 and RM-493-022 generalisable to NHS practice?	Section 3.2.2.2
Key Issue 3	How reliable and valid are the clinical effectiveness results for key outcomes reported by RM-493-023?	Section 3.2.5.1
Key Issue 4	What is the impact of potential bias arising from absence of randomised, controlled comparisons for key clinical outcomes at 52 weeks follow-up in RM-493-023?	Section 3.2.5.2
Key Issue 5	To what extent does the selective outcome reporting of exploratory outcomes reduce confidence in clinical effectiveness and cost-effectiveness results?	Section 3.2.5.2 and 3.2.6
Key Issue 6	All responders are assumed to move to the mild hyperphagia state, independent of change in BMI-Z / BMI.	Sections 4.2.2 and 4.2.6.3
Key Issue 7	Size of the treatment effect on BMI-Z in responders to setmelanotide in the paediatric population?	Section 4.2.6.2
Key Issue 8	BMI-Z / BMI reduction is extrapolated into the long-term	Section 4.2.6.2

Key Issue 9	Evidence sources for health-state utilities. Source of utilities from mapped PedsQL scores of an external overweight/obese child population, on which hyperphagia multipliers derived from vignette studies apply. The CS has reported clinically meaningful changes in PedsQL scores for the BBS population at baseline and after 1 year of treatment with setmelanotide, which can be mapped on EQ-5D utilities directly.	4.2.7.1, 4.2.7.2, 6.1.1**Error! Reference source not found.**, Appendix 3 (Section 0)
Key Issue 10	Utility multiplier for BBS patients due to non-obesity-related comorbidities.	4.2.7.3
Key Issue 11	Average number of carers for adult BBS patients	4.2.7.6

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

1. The EAG assume a higher annual rate of treatment discontinuation (for any reason) of 2% compared with the company's assumption of 1%. This EAG prefer this high rate based on data from the company's study, and to capture waning of treatment effect in the longer term.
2. The company model patients hyperphagia (hunger) as mild, moderate, and severe states, and assume that all patients who respond to treatment will have mild hyperphagia. The EAG assume that a proportion of patients who respond will have moderate hyperphagia and the rest will have mild hyperphagia. The proportions in moderate and mild assumed by the EAG are based on data on changes in obesity (BMI-Z) from the company's study.
3. The EAG assume the effect of setmelanotide on obesity is to reduce BMI-Z class by [redacted]-level for the paediatric BBS population compared with a reduction of [redacted]-levels in the companys model. The EAG consider this to better reflect the data from the company's study.
4. The EAG assume that an average of 0.5 carers per adult patient compared with the companys assumption of 1 carer per adult patient
5. The EAG assumes that patients taking setmelanotide will have their monitoring visits in secondary care weight-management clinics whereas the company assumes these are in primary care. The EAG assumes 1 more monitoring visit for setmelanotide compared with best supportive care in the second and subsequent years, whereas the company assumes there will be less visits for setmelanotide.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Decreasing hyperphagia
- Reducing BMI
- Improving obesity-related comorbidity profile and HRQoL related to comorbidity
- Decreasing carer burden

Overall, the technology is modelled to affect costs by:

- The treatment cost of setmelanotide
- Reduced costs associated with lower obesity levels
- Reduced costs associated with comorbidities
- lower annual monitoring costs in the second and subsequent years of use

The modelling assumptions that have the greatest effect on the ICER are:

- Severity of hyperphagia in population of patients treated with setmelanotide
- The treatment effect on hyperphagia
- The BBS specific utility multiplier for non-obesity related quality of life
- The treatment effect on obesity (BMI-Z) in paediatrics
- The average number of carers per adult patient

1.3 The decision problem: summary of the EAG's key issues

Key Issue 1: In the absence of a validated measure of hyperphagia, how will BBS patients with severe hyperphagia be identified in clinical practice?

Report section	Sections 2.2, 4.2.3, and 6.1
Description of issue and why the EAG has identified it as important	The population addressed in the company submission (CS) is narrower than the NICE scope and the marketing authorisation. The CS focuses on a subgroup of Bardet-Biedel Syndrome (BBS) patients with severe hyperphagia. However, severity of hyperphagia was not an eligibility criterion for recruitment to the company trials, nor was hyperphagia measured as an outcome. There is a large quality of life benefit gained by patients moving between the severe and mild utility states, which would be lower in patients starting with moderate hyperphagia. This will translate into a smaller gain in quality adjusted life years (QALYs) and a higher ICER. Initial hyperphagia state is the factor that has the biggest impact on the ICER in the company's deterministic sensitivity analysis.
What alternative approach has the EAG suggested?	The EAG ran a scenario analysis where a proportion (40%) of patients begin the model with moderate hyperphagia, and the rest (60%) with severe

	hyperphagia. The proportions of moderate and severe were taken from the company's response to clarification questions.
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases from £194,072 in the company's updated base-case to £230,084 when a proportion of patients have moderate hyperphagia.
What additional evidence or analyses might help to resolve this key issue?	Clarity on how BBS patients with severe hyperphagia will be identified in practice.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 2: Are the findings of studies RM-493-023 and RM-493-022 generalisable to NHS practice?

Report section	Section 3.2.2.2
Description of issue and why the EAG has identified it as important	Results from RM-493-023 and RM-493-022 are of uncertain generalisability to an NHS population, due to questions regarding similarity of participant characteristics across countries and the very small sample size of participants from the UK. Only 2 UK based patients were included in the main efficacy study RM-493-023 and extension study RM-493-022 and individual participant data is not reported in the CS.
What alternative approach has the EAG suggested?	BBS is a rare disease and study sample sizes are small. However, the company should demonstrate how participants in the two main clinical studies are representative of the BBS population in the UK, in terms of key participant characteristics.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	The CRIBBS registry may be a useful resource for further data on characteristics of UK based BBS patients.

Key Issue 3: How reliable and valid are the clinical effectiveness results for key outcomes reported by RM-493-023?

Report section	Section 3.2.5.1

Description of issue and why the EAG has identified it as important	There are reporting inconsistencies noted within the CS and across publications associated with the CS. For example, the CS includes contradictory statements regarding the use of specific outcomes in the economic model, and the extent of imputed data for the key clinical effectiveness outcomes. Due to the small sample sizes involved – especially for the post hoc subgroup analyses informing the economic model – the absence of information on proportions of imputed endpoint data at 52-weeks increases the uncertainty in the robustness of clinical effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG requested additional data to appraise the baseline characteristics of participants with missing observations/outcomes vs those without missing data. The proportions of missing data at 52 weeks were also requested But a response to the request was not provided.
What is the expected effect on the cost-effectiveness estimates?	Incomplete, inconsistent, or missing outcome data can generate a misleading ICER.
What additional evidence or analyses might help to resolve this key issue?	The 52 week follow up information requested in clarification questions A16 and A17 could be provided for the EAG to evaluate. Further information on the multiple imputation approach and pattern of data missingness by outcome/ observations could be provided so the EAG can assess the appropriateness of the approach taken, given the small sample sizes involved.

Key Issue 4: What is the impact of potential bias arising from absence of randomised, controlled comparisons for key clinical outcomes at 52 weeks follow-up in RM-493-023?

Report section	Section 3.2.5.2
Description of issue and why the EAG has identified it as important	The main study clinical outcomes and those informing the cost-effectiveness analysis are at serious risk of bias. At 52-weeks follow-up, the data are not from a randomised comparison but are considered as arising from an uncontrolled, before-after study. Non-randomised evidence is less reliable than randomised evidence for establishing causal effects and treatment effects may be overestimated. In the absence of a control-group, it is not possible to conclude that the observed treatment effect is entirely attributable to setmelanotide. There is some evidence of a placebo

	effect for hunger and BMI outcomes at 14 weeks, which is possibly due to "regression to the mean" effect, which would also affect for the main treatment effect outcomes at 52 weeks for those who start on setmelanotide (although would be controlled for in those who started on placebo).
What alternative approach has the EAG suggested?	The EAG suggests an adjustment for placebo / regression to the mean effects should be conducted for the 52 week outcome and adjusted for as appropriate. The EAG was unable to conduct this analysis without access to the data.
What is the expected effect on the cost-effectiveness estimates?	If the size of the treatment effect is attenuated for BMI and BMI-Z, then the ICER estimates will be larger (see Key Issue 7).
What additional evidence or analyses might help to resolve this key issue?	Ideally a randomised controlled trial with longer follow-up during the randomised period, is needed to reliably estimate causal effects. In the absence of this, an exploration of an adjustment for placebo / regression to the mean effects should be conducted for the 52 week outcome and adjusted for as appropriate.

Key Issue 5: To what extent does the selective outcome reporting of exploratory outcomes reduce confidence in clinical effectiveness and cost-effectiveness results?

Report section	Section 3.2.5.2 and 3.2.6
Description of issue and why the EAG has identified it as important	Selective outcome reporting is a concern in the CS. Full, up to date, study protocols (including the amendment update for exploratory outcomes) were not accessible for either RM-493-023 or RM-493-022. Selective outcome reporting in the CS cannot be ruled out, especially for exploratory weight and hunger outcomes (as these are not listed in the published trial protocol) and for HRQoL outcomes which are partially and inconsistently reported in the CS. It is not clear if the protocol amendment made part-way through study RM-493-23, and which introduced the additional exploratory outcomes, was made after the results from the first 'pivotal' cohort of participants were known.
What alternative approach has the EAG suggested?	Access to the updated study protocol to determine the likely impact of selective reporting. Using the HRQoL data collected directly from the main trial.

What is the expected effect on the cost-effectiveness estimates?	Hunger outcomes did not directly inform the economic model. Data used to estimate HRQoL in the model was sourced exclusively from an external non-BBS cohort study (more details in key issue 9). It is possible that using HRQoL data collected directly from the trial would produce lower QALY gains accrued for the setmelanotide group than the current model predicts. This would have the potential to increase the ICERs substantially.
What additional evidence or analyses might help to resolve this key issue?	Clearer, transparent reporting, including all the scales and subscales of HRQoL measures collected for all children and adults in the trials, and provision of the updated study protocols for EAG to assess.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Key Issue 6: All responders are assumed to move to the mild hyperphagia state, independent of change in BMI-Z / BMI.

Report section	Sections 4.2.2 and 4.2.6.3
Description of issue and why the EAG has identified it as important	The company assumes that all patients who respond will move from severe to mild hyperphagia and remain in the mild state whilst on treatment. This is modelled independently of change in BMI-Z / BMI. There is a large utility benefit between the severe and mild utility states, and so this assumption leads to a large contribution to the quality of life benefits from setmelanotide, and a large impact on the ICER.
What alternative approach has the EAG suggested?	The EAG proposes an alternative where responders can move to either a moderate or mild hyperphagia state, where the proportions in each are based on the proportion of responders who have a [redacted] or [redacted] class reduction in BMI-Z. The EAG use this assumption in their base-case.
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases from £194,072 in the company's updated base-case to £217,863 when a proportion of responders move to the moderate hyperphagia state.
What additional evidence or analyses might help to resolve this key issue?	The company did not directly measure hyperphagia in their study, however they did collect data on daily hunger score, global hunger and a caregiver completed questionnaire (Food Problem Diary). Further data to enable a mapping between hunger

	score and hyperphagia state (on which utilities are based) would enable the proportion of patients moving to moderate or mild hyperphagia to be estimated.

Key Issue 7: Size of the treatment effect on BMI-Z in responders to setmelanotide in the paediatric population?

Report section	Section 4.2.7.1
Description of issue and why the EAG has identified it as important	The small sample of study RM-493-023 means there is a high level of uncertainty around the number of BMI-Z class changes. The company assumes a reduction in BMI-Z of [redacted] classes for responders to setmelanotide in the paediatric population. The EAG note that there is variability in movement between BMI-Z classes in patients in study RM-493-023, and felt this was consistent with a [redacted] class reduction in BMI-Z. Change in BMI-Z class is assumed to persist into the long-term whilst patients are on treatment, and leads to reductions in obesity-related co-morbidities, which in turn improve length and quality of life and lower costs. This has a large impact on the ICER.
What alternative approach has the EAG suggested?	The EAG prefer to use a [redacted] class reduction in BMI-Z for paediatric patients in line with data from study RM-493-023, and use this in their base-case.
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases from £194,072 in the company's updated base-case to £207,320 when a [redacted] class reduction in BMI-Z is assumed for paediatric patients.
What additional evidence or analyses might help to resolve this key issue?	Ideally, a larger randomised controlled trial is needed to more reliably estimate the change in BMI-Z for setmelanotide compared with a control. An alternative would be to use mean change in BMI-Z from the trial and apply this to an assumed continuous distribution of BMI-Z at baseline (e.g Normal or log-Normal). The resulting distribution can then be used to estimate the proportion of patients in each BMI-Z class.

Key Issue 8: BMI-Z / BMI reduction is extrapolated into the long-term

Report section	Section 4.2.6.2

Description of issue and why the EAG has identified it as important	The model assumes that patients continue to stay in the same reduced BMI-Z / BMI class for the remainder of their life whilst taking setmelanotide. The companys extension study RM-493-22 shows a sustained reduction in BMI-Z / BMI at 36 months. However, it is uncertain how long the BMI-Z / BMI reduction will persist beyond that time, before some waning of effect occurs. Reduced BMI-Z class leads to reductions in obesity-related co-morbidities, which in turn leads to improved length and quality of life and lower costs. This has a large impact on the ICER.
What alternative approach has the EAG suggested?	The EAG explored a scenario where 1% of patients per year return to their original BMI-Z / BMI class, but remain on treatment and retain their hyperphagia benefit.
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases from £194,072 in the company's updated base-case to £200,092 when a 1% waning effect is applied.
What additional evidence or analyses might help to resolve this key issue?	Study RM-493-22 is on-going, and so will in time produce data on the longer-term effects of setmelanotide on BMI-Z / BMI. However, we note this is a single arm study with no control group, so it will not be possible to distinguish the contribution of setmelanotide on long-term changes in BMI-Z / BMI from the impact of other factors.

Key Issue 9: Evidence sources for health-state utilities

Report section	4.2.7.1, 4.2.7.2, 6.1.1, Appendix 3 (Section 0)
Description of issue and why the EAG has identified it as important	The CS argues that EQ-5D estimates collected from the RM-049-023 trial patients would not be sensitive to pick up the effects on hyperphagia on the BBS population, which the EAG agrees with. The company did however collect data using additional health-related quality of life (HRQoL) tools, but limited results are presented in the CS and the data are not used in the company's model. The CS sources utilities by BMI-Z / BMI exclusively from external cohort studies of children and adults without BBS or hyperphagia. These were mapped onto EQ-5D utilities using standard methods. There was no literature review performed to inform the choice of external HRQoL data sources.

	The CS then used utility multipliers to adjust the for the BBS population and for hyperphagia. The hyperphagia multiplier relies on a vignette study, and there was no source provided to inform the BBS multiplier (see Key Issue 10). The company has since published HRQoL estimates for patients in the RM-049-023 study and conclude that the HRQoL improvements observed were large and clinically meaningful.[1] These results could have been used to inform the current model to avoid the need to rely on hyperphagia and BBS multipliers. The EAG was unable to do this because the study does not report results on all the subscales required for the EAG to map these results.[1]
What alternative approach has the EAG suggested?	The EAG has proposed an alternative method to inform utilities in the model that would have avoid the use of BBS and hyperphagia multipliers. This method uses estimates of mapped PedsQL scores onto utilities from the literature that are similar to the baseline and follow-up scores of the RM-049-023 trial responders (Appendix 3, Section 0). However, the EAG is still missing data to estimate utilities for the adult population. The model would have required complex adaptations, relying on numerous assumptions, which the EAG was not comfortable to make.
What is the expected effect on the cost-effectiveness estimates?	It is possible that the current hyperphagia and BBS multipliers used to adapt utilities from the general obese population are artificially inflating the HRQoL benefits from setmelanotide. Given that setmelanotide accrues [redacted] QALYs over the lifetime of the patient in the CS base case, small decreases in QALY gains could increase the ICER considerably.
What additional evidence or analyses might help to resolve this key issue?	The model could be adapted to use HRQoL data for the BBS population on setmelanotide. To explore the alternative approach, the EAG would require results for all HRQoL data collected in the RM-049-023 and RM-049-022 studies, by age and BMI category, for responders and non-responders, at baseline, 14-weeks and 12 months follow-up.

	The EAG suggested sensitivity analyses using trial HRQoL sources at the decision problem meeting. The EAG requested the company to provide mapped PedsQL scores for trial children onto EQ-5D utilities in clarification questions, which they could do using the external Riazi 2010 study. The company did not provide those sensitivity analyses or mapped utilities. The article where the company publishes HRQoL estimates[1] does not report results on all the subscales required for the EAG to map these results.

Key Issue 10: Utility multiplier for BBS patients due to non-obesity-related comorbidities.

Report section	4.2.7.3
Description of issue and why the EAG has identified it as important	A BBS specific utility multiplier of 0.8 was applied to capture the impact of non-obesity-related co-morbidities for BBS patients. In the absence of any data, the company assume a value of 0.8. This value is arbitrary and does have a large impact on the ICER. The BBS-specific multiplier is applied because utility data for the model is sourced from an external population without BBS. The EAG agree that in this case it is appropriate to apply a BBS specific multiplier, but it is unclear what the value of the multiplier should be.
What alternative approach has the EAG suggested?	The EAG have presented scenarios to different values for the BBS specific utility multipler (0.7 and 0.9).
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases as the BBS specific utility multiplier decreases from £179,429 (multiplier = 0.9), to £194,072 (multiplier=0.8, the company's updated base-case) to £213,869 (multiplier=0.7).
What additional evidence or analyses might help to resolve this key issue?	Estimating utilities directly from HRQoL data from the RM-493-023 trial patients would avoid the need to apply an arbitrary multiplier, given that trial patients have BBS (see Key Issue 9). It may be possible to estimate a BBS specific utility multiplier using data from a matched cohort of non-BBS people where HRQoL data are available. Again, this would require having HRQoL for a BBS population available, which if taken from the trial

	data could be used directly and avoid the need for a multiplier. An alternative would be to use a similar approach used by the company for obesity-related comorbidities, based on prevalence of non-obesity-related comorbidities in BBS patients and literature-based disutilities.

Key Issue 11: Average number of carers for adult BBS patients

Report section	Section 4.2.7.6
Description of issue and why the EAG has identified it as important	The company assume 1 carer per adult BBS patient. However, in practise this will vary depending on the co-morbidity burden of the patient. Not all adult BBS patients require a carer, although some with severe disability may require upto 2 carers. The model assumes a disutility per carer over the patients life-time, which has a large impact on Quality Adjusted Life Years (QALYs) and hence on the ICER.
What alternative approach has the EAG suggested?	The EAG heard that the average number of carers will be less than 1 and that 0.5 may be a more reasonable number to assume. The EAG ran scenarios with values of 0.8 and 0.5 and used 0.5 in its base-case.
What is the expected effect on the cost-effectiveness estimates?	The probabilistic ICER for the paediatric population increases as the average number of carers for adult BBS patients reduced from £194,072 (number carers=1, the company's updated base-case) to £197,532 (number carers=0.8) to £205,202 (number carers=0.5).
What additional evidence or analyses might help to resolve this key issue?	This could be resolved through a survey of BBS patients.

1.6 Other key issues: summary of the EAG's view

The EAG did not identify any further key issues. Summary of EAG's preferred assumptions and resulting ICER are provided in Table 2.

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)

Probabilistic results (for the paediatric population)			
Company's updated base case after clarifications.	[redacted]	[redacted]	£194,072
Assumption 1: treatment discontinuation rate of 2%. Section 4.2.6.4	[redacted]	[redacted]	£191,953 (-1.09%)
Assumption 2 : Treatment effect on severe hyperphagia with [redacted] moving to mild and [redacted] to moderate hyperphagia. Key Issue 6. Sections 4.2.2 and 4.2.6.3	[redacted]	[redacted]	£217,863 (+12.26%)
Assumption 3 : Treatment effect [redacted] level reduction in BMI-Z class for the paediatric BBS population. Key Issue 7. Section 4.2.7.1	[redacted]	[redacted]	£207,320 (+6.83%)
Assumption 4 : 0.5 care-givers per adult patient. Key Issue 11. Section 4.2.7.6	[redacted]	[redacted]	£197,532 (+1.78%)
Assumption 5 : Secondary/tertiary care costs for monitoring visits in weight-management clinics setmelanotide group in the first and subsequent years. Section 4.2.8.2	[redacted]	[redacted]	£196,088 (+1.04%)
EAG's Preferred base case, assumptions 1 + 2 + 3 + 4 +5	[redacted]	[redacted]	£246,901 (+27.22%)

Modelling errors identified by the EAG are described in the clarification questions and section 5.5, and were corrected by the company in their updated model. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6 of the EAG report.

2 INTRODUCTION AND BACKGROUND

This report provides a critique of the evidence submitted by the company Rhythm Pharmaceuticals in support of setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (BBS). It considers the company evidence submission[2] and the company's executable model received on 27/1/23. It also considers the company's response and updated mode following clarification questions from the EAG received on 8/3/23.

2.1 Critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention.

Full details of the technology, its mechanisms of action, and the intended positioning of the intervention are described in section B.1 of the company submission (CS) [2].

BBS is a rare autosomal recessive disease, confirmed in the UK using a genotyping panel test. 72% to 92% of people with BBS will be affected by obesity. The hypothalamic leptin-melanocortin signalling pathway is responsible for regulation of appetite and satiety and is believed to be disrupted in people with BBS. setmelanotide is an melanocortin 4 receptor (MC4R) agonist, which restores lost signalling and reduces hyperphagia associated with BBS (extreme insatiable hunger and shortened satiety after eating). The EAG agrees with the CS that reduction in appetite and increased satiety length after eating will result in weight loss.

The CS seeks approval for setmelanotide in both paediatric and adult populations. Clinical advice sought by the EAG agreed that this was appropriate. The CS states that the current standard treatment for the management of obesity in England, in both adults and children, is lifestyle modification and dietary advice. The EAG's clinical advisors agreed with this position. However, the EAG's clinical advisors disagreed that ongoing management for patients administered setmelanotide would take place within primary care. Rather, they considered it more likely that ongoing management would take place in secondary care services, local to the BBS patient, and that this would be supported by one of the specialist BBS centres in Birmingham or London. The implications of this for costs are discussed further in section 4.2.8.2.

2.2 Critique of company's definition of decision problem

Table 3 summarises the decision problem as outlined in the NICE scope, how this was addressed in the company submission, and summarises the EAG's critique. The company's definition of the decision problem does not fully match the final NICE scope. In particular, the population addressed in the CS is narrower than the final scope and only includes BBS patients with severe hyperphagia. The EAG notes that severity of hyperphagia was not measured in the studies informing the CS (RM-493-023 and RM-493-022). Instead, the CS assumes that patients responding to setmelanotide were those with (unmeasured) severe hyperphagia at baseline. The company response to EAG clarification question A1 notes that hunger scores alone are not a meaningful metric in BBS patients [3]. The EAG is unsure how a

subgroup of BBS patients with severe hyperphagia would be distinguished in clinical practice.

Key Issue 1: in the absence of a validated measure of hyperphagia, how will BBS patients with severe hyperphagia be identified in clinical practice?

3 CLINICAL EFFECTIVENESS

The CS reports findings from two studies to support the clinical effectiveness of setmelanotide in patients with Bardet-Biedl syndrome (BBS). The main company trial, RM-493-023, is a multicentre phase 3 study, including a randomised double blind, placebo-controlled period [4]. The second study is an open-label extension study, RM-493-022 [5]. Although the CS reports findings from RM-493-022, the EAG note that the study is ongoing (CS, Table 21) and the results do not inform the economic model. In the factual accuracy response, the company noted that although the study is ongoing, as reported on ClinicalTrials.gov, most BBS patients are no longer in the study and no new data output is anticipated for BBS patients from this study.

A third study, RM-493-014[6], is also reported in Appendix N of the CS [7]. RM-493-014 is a phase 2 study, from which participants were eligible to join the open-label extension study, RM-493-022. However, RM-493-014 does not contribute efficacy data to the CS and is not discussed further in the EAG's critique.

The company also included a systematic literature review of clinical effectiveness to synthesise the evidence from clinical trials or observational studies. The EAG critique is reported in 3.3 of this report.

Table 3 Summary of decision problem and EAG comments

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	People aged ≥6 years with obesity and hyperphagia with BBS and the following obesity markers: • People aged ≥18: body mass index (BMI) of ≥30 kg/m2 • People aged ≤17: weight of ≥97th percentile for age on growth chart assessment.	People aged ≥6 years with obesity and severe hyperphagia with BBS and the following obesity markers: • People aged ≥18: BMI of ≥30 kg/m2 • People aged ≤17: weight of ≥97th percentile for age on growth chart assessment.	The rationale for the difference is specified in Section B.1.1 of the CS.	The population addressed in the CS is narrower than the NICE scope and focuses on a subgroup of BBS patients with severe hyperphagia. A justification was provided in clarification question A1 [3]. The company stated it appropriate to restrict the CS to this subgroup due to the cost-effectiveness and clinical benefit of setmelanotide in these patients. However, as no clinical assessment tool is available to measure hyperphagia severity in this population, and severity was not measured at baseline in study RM-493-023, the EAG notes the decision to narrow the population appears to be post hoc. Eligibility criteria of the main trial (RM-493-023) is different to the scope: *"patients aged ≥6 years with a clinical diagnosis of BBS or AS, and obesity defined as BMI ≥97th percentile for age and sex on growth charts for those aged*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
				6 to <16 years". The EAG does not consider this discrepancy will impact the generalisability of the results.
Intervention	Setmelanotide	Setmelanotide in combination with diet and exercise advice	Setmelanotide is not expected to replace diet and exercise advice for treatment of obese patients with BBS, rather it is expected to improve the impact of these interventions.	The intervention addressed in the CS is setmelanotide in combination with diet and exercise advice. However, the clinical trial evidence submitted in the CS is from a trial of setmelanotide only. Clarification question A10 confirms that patients in study RM-493-023 were not receiving weight-loss advice as part of the study. Clinical advice sought by the EAG considered the proposed positioning of setmelanotide as an addition to, and not a replacement for, standard management, to be appropriate.
Comparator(s)	• Established clinical management without setmelanotide (including a reduced calorie diet and increased physical activity) • Bariatric surgery	• Established clinical management without setmelanotide (including a reduced calorie diet and increased physical activity)	Bariatric surgery is not recommended for rare genetic disease of obesity (RGDO) patients and does not address the genetic impairment and resulting insatiable hunger. It is	Clinical advice to the EAG indicated that bariatric surgery is not generally suitable for this population. The EAG considers the exclusion of bariatric surgery to be appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
			also not a suitable treatment option for patients with cognitive impairment	
Outcomes	Outcome measures to be considered: • BMI and BMI Z-score • Weight loss • Percent body fat • Waist circumference • Hunger • Incidence of type 2 diabetes (T2DM) • Cardiovascular events • Mortality • Co-morbidities associated with early onset severe obesity including cancer • Adverse effects of treatment • Health-related quality of life (HRQoL) for patients and carers	Outcome measures to be considered: • BMI and BMI Z-score • Weight loss • Percent body fat • Waist circumference • Hunger • Incidence of T2DM • Cardiovascular events • Mortality • Mortality effect associated with early onset severe obesity • Adverse effects of treatment • HRQoL for patients and carers		The majority of outcomes reported in the CS match the NICE scope. The EAG note the discrepancy between the NICE scope: '*Co-morbidities* associated with early onset severe obesity including cancer and the CS '*Mortality effect* associated with early onset severe obesity' as an outcome. The EAG also note that:, incidence of T2DM, cardiovascular events, and mortality effect associated with early onset severe obesity were measured in the main company trial (RM-493-023) but are not directly reported on in the CS. HRQoL was measured but only partially, and inconsistently, reported in the CS.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	The model does not use EQ5D data for quality of life, instead, hyperphagia quality of life	EQ5D was not deemed sufficiently sensitive to capture	The EAG agrees that the EQ-5D may not be sensitive to capture

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
	expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement	multipliers from a vignette study (Appendix O) are used. Other utilities were derived from external sources or based on assumption. A managed access proposal is not being submitted.	the impact of hyperphagia on quality of life	the health benefits from hyperphagia, but other sources of HRQoL data would have been available to the company for use in the model. Those would have been superior sources in the hierarchy of preference-based HRQoL measures. Model estimates for utilities were derived from external sources. This follows the previous submission for HST21. The lifetime horizon assumes no waning of treatment effect, which may be optimistic for obesity treatments.
Subgroups	None specified	Paediatric BBS patients with severe hyperphagia Adult BBS patients with severe hyperphagia	Differences in study outcome are seen between adult and paediatric subgroups. Though the submission presents subgroup analyses for paediatric and adult patients,	A severe hyperphagia subgroup was not specified in the NICE scope. The EAG consider the separate reporting of results for adult and paediatric populations to be appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
			approval is sought for patients of all ages	
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The submission focuses on a severe hyperphagia sub-population of the technology's marketing authorisation.	This position is narrower than the marketing authorisation because: • This population optimises the cost effectiveness of setmelanotide because patients with severe hyperphagia experience significantly greater impact on their quality of life than those with mild or moderate hyperphagia. • This population therefore reflects where setmelanotide provides the most clinical benefit.	There is no validated tool to assess severity of hyperphagia in BBS patients. The EAG's clinical advice indicated that in practice BMI/BMIz together with an informal assessment of hyperphagia would be used to determine appropriateness of treatment rather than hyperphagia. Therefore, setmelanotide may be used in a wider population of obese BBS patients. See also comments in population section above.

BBS = Bardet-Biedl syndrome, BMI = body mass index, EAG = external assessment group

3.1 Overview of evidence reported in company submission.

Table 4 provides an overview of the primary and key secondary clinical efficacy outcomes reported in the company submission, the data sources used, if and how the outcome informed the economic model, whether the outcome is within the NICE scope, and whether the weight loss outcomes are recommended by the European Medicines Agency (EMA).[8] Two post-hoc outcomes used to inform the economic model are also described.

3.2 Critique of evidence of clinical effectiveness

3.2.1 Study design

Table 5 describes the study design, interventions, inclusion criteria, and outcomes for the two main studies reported in the CS: study RM-493-023 (NCT03746522)[4] and study RM-493-022 (NCT03651765)[5].

Study RM-493-023 had three treatment periods. The first was a 14-week, double-blind, placebo-controlled period, in which participants were randomised to receive setmelanotide or placebo once daily via subcutaneous injection. At the end of period one, all participants entered period two, which was a 38-week open-label treatment period in which all participants received setmelanotide. To maintain blinding, an upward dose escalation to 3mg of setmelanotide for all patients was completed in the first two weeks of period two. Treatment period 3 was a further 14-week open-label period in which all patients continued to receive setmelanotide. This allowed participants who had been initially randomised to placebo, to receive 52 weeks of setmelanotide treatment. See section 3.2.5 of this report for the EAG's risk of bias assessment and critique of study endpoints.

Two cohorts of patients were recruited to study RM-493-023:

- 'Pivotal cohort': the initial cohort of 32 BBS patients enrolled into the study. After completion of study RM-493-023, the pivotal cohort were eligible to enter the open-label extension study, RM-493-022. Efficacy results at 52-weeks follow-up are only reported for the pivotal cohort.
- 'Supplemental cohort': an additional cohort comprising 12 BBS patients. 'Supplemental' participants were permitted to exit RM-493-023 before the 52-week endpoint and enrol in the extension study, RM-493-022. Both pivotal and supplemental cohort data are used in the 14-week analyses reported in the CS.

All supplemental participants were recruited after a protocol variation had been approved. (CS, Section B.2.3.1)

Study RM-493-022 is an ongoing, open-label extension study following up participants over a further 2 years setmelanotide treatment. Participants were previously enrolled in either RM-493-023 or RM-493-014. Figure 4 in the CS provides a summary of the study design.

Table 4 Overview of clinical evidence included in the company submission.

Key Outcomes	Outcome	Treatment comparison	Data source	In economic model?	Listed by EMA ?	In NICE scope?
Proportion of patients aged ≥12 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks.	Primary	Single arm, non-randomised (no comparator)	Trial RM-493-023 Company submission (Table 23)	No	Yes	Yes
Mean percent change in body weight from baseline in patients aged ≥12 years after ~52 weeks of treatment.	Secondary	Single arm (no comparator)	Trial RM-493-023 Not reported (CS reports for ≥18 years)	No	Yes	Yes
Percent change in daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment.	Secondary	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 27)	No	NA	Yes
The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks treatment.	Secondary	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 28)	No	NA	Yes
Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment.	Secondary	Direct, randomised (vs. placebo)	Trial RM-493-023 Not reported (CS reports for ≥18 years)	No	Yes	Yes
Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment.	Secondary	Direct, randomised (vs. placebo)	Trial RM-493-023 Company submission (Table 24)	No	NA	Yes
Proportion of patients aged <18 years achieving a BMI Z-score reduction of 0.2 or 0.3 points after 52 weeks	Post hoc	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 31)	Yes	No	Yes
BMI shift data for individual patients aged ≥18 years who were classified as 52-week responders	Post hoc	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 34)	Yes	No	No
BMI Z-score shift data for individual patients aged <18 years who were classified as 52-week responders	Post hoc	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 35)	Yes	No	No
Proportion of patients aged ≥18 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks	Post hoc	Single arm (no comparator)	Trial RM-493-023 Company submission (Table 23)	No	Yes	Yes

BBS=Bardet-Biedl syndrome, BMI=Body Mass Index, CS=company submission; EMA = European Medicines Agency

Table 5: Study details for the two main studies in the CS (RM-493-023 and RM-493-022)

	RM-493-023	RM-493-022
Design	Phase III, 14-week randomised, double-blind, placebo-controlled treatment period. Followed by an open-label extension period of up to 52 weeks during which all participants received setmelanotide.	Phase III, open-label extension study, providing 2 years additional setmelanotide treatment for patients who completed a prior index study (RM-493-023 or RM-493-014)
Intervention	Setmelanotide (n=22) Placebo (n=22)	Setmelanotide (n=42)
Inclusion criteria	≥6 years of age	≥6 years of age
	A BBS clinical diagnosis, as per Beales 1999	Completed participation and demonstrated adequate safety in a previous setmelanotide study for obesity (RM-493-023 or RM-493-014).
	Have obesity (BMI ≥30 kg/m2 for patients aged ≥16 years or weight ≥97th percentile for age and sex on the growth chart for patients aged 6 to 16 years)	
Location	US, Canada, UK, France, and Spain	US, Canada, UK, France, and Spain
Primary Outcomes	Primary: proportion of patients aged ≥12 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks.	Primary: characterise the safety and tolerability of setmelanotide, assessed by the frequency and severity of AEs; changes in physical examination, electrocardiogram (ECG), vital sign, and laboratory evaluations; and the occurrence of injection site reactions.
Key secondary outcomes described in CS	1. Mean percent change in body weight from baseline in patients aged ≥12 years after ~52 weeks of treatment. 2. Percent change in daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment. 3. The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks of treatment. 4. Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment. 5. Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment.	No secondary outcomes listed

AEs=adverse events, BBS=Bardet-Biedl syndrome, BMI=Body Mass Index

3.2.2 Patients

3.2.2.1 Eligibility criteria for RM-493-023 and RM-493-022

Full eligibility criteria for studies RM-493-023 and RM-493-022 are listed in section B.2.3.1 of the CS. For the main trial, RM-493-023, eligible participants were aged 6 years or older with a clinical diagnosis of BBS or AS and who had obesity. Obesity was defined as a BMI ≥30 kg/m^2 for participants aged ≥16 years. For participants aged 6 to 15 years, obesity was defined as having weight ≥97th percentile for age and sex on growth chart assessment. The EAG notes this differs from the decision problem specified by the NICE scope, for which the age cut offs were ≥18 years and ≤17 years (see Table 3). It is not anticipated that this difference would affect the validity or generalisability of the study results.

For the extension study, RM-493-022, eligible participants were aged 6 years or older and who had completed a prior 'index' trial with setmelanotide (either RM-493-023 or RM-493-014). Only participants who had demonstrated clinical efficacy 'response' were eligible for the extension study.

Table 6 Baseline characteristics for Study RM-493-023 and RM-493-022 (reproduced from CS Table 12 and Appendix M)

	Study RM-493-023 (N=44)	Study RM-493-022 (N=42)
Age (Mean, SD)	20.00 (11.2)	[redacted]
Sex (Female %)	54.5	[redacted]
Race (%)	White: 77.3 Black or African American: 4.5 Asian: 2.3 Other: 15.9	White: [redacted] Black or African American: [redacted] Asian: [redacted] Other: [redacted]
Ethnicity (%)	Non-Hispanic and non-Latin: 84.1 Hispanic or Latin: 2.3 Not reported: 6.8 Unknown: 6.8	Non-Hispanic and non-Latin: [redacted] Hispanic or Latin: [redacted] Unknown: [redacted]
Weight, kg (Mean, SD)	108.5 (33.5)	Index Study$^+$: [redacted] Extension Study$^\wedge$: [redacted]
BMI, kg/m^2 (Mean, SD)	41.5 (9.9)	Index Study$^+$: [redacted] Extension Study$^\wedge$: [redacted]
Most/worst hunger (Mean, SD)	6.8 (1.8)	NR

$^+$ baseline value from the 'index' study to which participant was originally recruited (either RM-493-023 or RM-493-014) before joining extension study RM0-493-022.

$^\wedge$ baseline value as measured on recruitment to extension study RM-493-022.

3.2.2.2 Baseline characteristics of participants in RM-493-023 and RM-493-022

3.2.3 Baseline characteristics for RM-493-023 and RM-493-022 are outlined in Patients

3.2.3.1 Eligibility criteria for RM-493-023 and RM-493-022

Full eligibility criteria for studies RM-493-023 and RM-493-022 are listed in section B.2.3.1 of the CS. For the main trial, RM-493-023, eligible participants were aged 6 years or older with a clinical diagnosis of BBS or AS and who had obesity. Obesity was defined as a BMI

≥30 kg/m^2 for participants aged ≥16 years. For participants aged 6 to 15 years, obesity was defined as having weight ≥97th percentile for age and sex on growth chart assessment. The EAG notes this differs from the decision problem specified by the NICE scope, for which the age cut offs were ≥18 years and ≤17 years (see Table 3). It is not anticipated that this difference would affect the validity or generalisability of the study results.

For the extension study, RM-493-022, eligible participants were aged 6 years or older and who had completed a prior 'index' trial with setmelanotide (either RM-493-023 or RM-493-014). Only participants who had demonstrated clinical efficacy 'response' were eligible for the extension study.

Table 6. The EAG's clinical advisors considered participants to be similar to UK patients in terms of baseline BMI. However, most participants were from the USA and only two participants in each study were from the United Kingdom. Due to these small numbers, the EAG highlights the potential lack of generalisability to England and NHS population. It is unclear whether the two UK participants enrolled in RM-493-023 are the same two UK patients enrolled in RM-493-022.

In response to clarification question A2, the company provided baseline characteristics for RM-493-023 by 'cohort' (i.e. by pivotal and supplemental patients) and by participants with ≥52 weeks and <52 weeks follow up[3]. Compared to those with <52 weeks follow up, participants with ≥52 weeks follow up, had a slightly higher [redacted] BMI and mean age at baseline were balanced between pivotal and supplemental patients. However, compared to the pivotal cohort, the supplemental cohort had a lower mean weight and a lower proportion of white, non-Hispanic, and non-Latin participants.

The EAG requested baseline characteristics for RM-493-022 to be stratified by the two index studies from which eligible participants were recruited (RM-493-023 and RM-493-014) (clarification question A5), however the company were unable to provide the data in the response window. Therefore, EAG are unable to determine whether patient characteristics in the extension study RM-493-022 differed by their earlier index study.

The EAG also requested baseline data for hyperphagia severity (clarification question A1). However, the company were not able to provide the data as hyperphagia was not assessed - quantitatively or qualitatively - in RM-493-023 nor RM-493-022. The company note that no clinical assessment tool has been validated for hyperphagia in BBS patients (clarification response, A1) [3]. As results could not be provided by baseline hyperphagia severity status, the EAG question the validity of study RM-493-023 for the population specified in the decision problem (see Table 3 of EAG report).

Key Issue 2: Are the findings of studies RM-493-023 and RM-493-022 generalisable to NHS practice?

3.2.4 Interventions

In both RM-493-023 and RM-493-022, setmelanotide was administered as a subcutaneous injection once daily by the patient/caregiver. In RM 493-023, participants were randomised to receive either setmelanotide or placebo, during the 14-week double-blind treatment period. Participants in the setmelanotide treatment arm followed a dose escalation schedule depending on age and this was matched for those in the placebo arm. Participants aged <16 years received a starting dose of 1.0mg once daily, increasing to 2.0mg after 1 week, and to 3.0mg after 2 weeks (depending on safety and tolerability). Participants aged ≥16 years received a starting dose of 2.0mg once daily which was increased to 3.0mg after 1 week (based on tolerability). Placebo was administered via subcutaneous injection and matched the appearance of the setmelanotide solution. After 14 weeks, participants entered an open-label treatment period in which all received setmelanotide. A further 2-week dose escalation schedule was followed for all participants to maintain blinding.

Participants in extension study RM 493-022, continued taking the setmelanotide dose (0.5mg – 3.0mg) received on completion of their index study (RM 493-023 or RM 493-014). Dose level changes were permitted at any time in the study, based on safety or efficacy findings. In clarification question A5, the EAG requested baseline information stratified by each index study, however the company were unable to provide the data in the response window. The EAG is therefore unable to comment on whether baseline doses in RM-493-022 were comparable across the two index studies.

The intervention addressed in the CS (Table 3) is setmelanotide in combination with diet and exercise advice. However, it is unclear whether the effect of setmelanotide observed in RM-493-023 and RM-493-022 should be interpreted as the effect of setmelanotide alone, or in combination with diet and exercise. In response to clarification question A10 [3], the EAG note that the company's trials evaluated setmelanotide alone, and not setmelanotide plus diet and exercise. However, the company state that participants' diet and exercise programs were not to be changed compared to what was used at time of inclusion in the trial (paediatric patients received nutritional counselling to maintain proper growth). Details on how many trial participants were following external dietetic and exercise programs at the time of trial recruitment, what the content of those programs were, and whether they varied by centre or country, were not made available to the EAG.

Additionally, concomitant medications were permitted in both RM-493-023 and RM-493-022. In RM-493-023, protocol changes were made prior to recruitment of the supplemental cohort that permitted use of concomitant medications that theoretically could cause weight loss (e.g. GLP-1 receptor agonists), as long as the participants; (1) had used them at a stable dose for at least 3 months prior to randomisation, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable during the study. The protocol changes impacted the supplemental cohort only, and clarification response A8 states that [redacted] patient was taking an GLP-1 receptor agonist. The EAG consider this to have a

minimal impact on efficacy results reported in the CS. In study RM-493-022 (CS, B.2.3.1) medications that could impact on efficacy assessments were not permitted. This included anorectic agents or drugs with anorexia as a non-rare side effect and low-threshold drugs.

3.2.5 Efficacy outcomes and risk of bias assessment

3.2.5.1 Study RM 493-023

Study RM-493-023 included both BBS and AS patients. For the purposes of the CS, outcomes are reported for a post-hoc subgroup of BBS patients only. The CS reports one primary outcome, five 'key' secondary outcomes, and 14 exploratory outcomes for RM 493-023 (CS, Section B.2.3.1). In addition, post hoc analyses to inform the economic model are also reported. Table 7 provides a summary of three planned analysis 'sets' for RM-493-023 and the number of participants contributing to each (as reported in CS, Figure 5). However, the primary statistical analyses were conducted at the end of period 2 (38-week open label) and for the outcomes considered at 52 weeks, only participants from the 'pivotal' cohort could be included. Outcomes at 14 weeks included participants from both the 'pivotal' and 'supplemental' cohorts. However, it is not clear that all 'pivotal' participants were included in analyses at 52 weeks, as claimed on page 55 of the CS (section B.2.4). The EAG note from Table 42 and 43 of the CS [2] that 18 participants did not have a full 52 weeks on the study (10 patients aged ≥18 years and 8 patients aged <18 years). Only 12 participants were recruited to the supplemental cohort (CS, Figure 5).

On page 61 of the CS, it is noted that *"a small proportion of patients randomised to placebo could have had less than ~52 weeks of setmelanotide treatment at the time of the primary analysis"* (Section B.2.4). For participants without 52 weeks follow-up data, a multiple imputation approach was used to impute measurements to a timepoint that approximated 52 weeks. Due to the limited information available in the CS, the EAG are not able to critique the statistical methodology used for imputation. However, the validity of multiple imputation relies on there being a sufficient number of participants with a full set of measurements across all outcomes and covariates of interest. As the CS does not explicitly report on the number of participants with imputed endpoint data and the validity of the imputation approach is therefore uncertain. In clarification question A16, the EAG requested baseline characteristics for participants whose follow-up data was imputed and for participants whose follow up data was not imputed [3]. However, the company was unable to provide the data and the EAG are unable to assess any differences in baseline characteristics between participants with a full 52 weeks and those without the full follow-up.

Table 7 Study RM-493-023 analysis set (Reproduced from Table 15, CS Document B[2])

Analysis set	Definition	Baseline for efficacy analyses	Use
Safety analysis set (SAS)	All patients who received at least 1 dose of a study drug (placebo or setmelanotide).	NA	Safety outcomes. Patient data were analysed according to the treatment received.

Full analysis set (FAS)	All patients who received at least 1 setmelanotide dose and provided 'baseline' data. N= 43 (CS, Figure 5)	Active treatment baseline (ATB): the last available measurement prior to the first dose of setmelanotide	Primary outcome and three secondary efficacy outcomes at 52 weeks only. "*The pivotal cohort therefore provides data for 52-week efficacy analyses"* (CS, B.2.4, pg 56). N=31 (CS, Figure 5) Multiple imputation used for missing data, but CS does not specify proportion of patients (or observations) with imputed data.
Placebo-controlled analysis set (PCAS)	All randomised patients who received at least 1 dose of placebo or setmelanotide and provided baseline data N= 44 (CS, Figure 5)	Placebo-controlled period baseline (PCPB): The last available measurement prior to the first dose of setmelanotide or placebo	Data from the 14-week placebo-controlled, double-blind period (Period 1). PCAS is used for two secondary outcomes. PCAS analyses were performed based on patients as initially randomised.

CS= company submission; NA=not applicable.

A multiple imputation approach was also used for participants with missing observations for other reasons (loss to follow up, early discontinuation, missed visit, AEs etc). For primary and secondary analyses, however, imputed values were replaced with the patient's baseline value.

The clinical effectiveness results for RM-493-023 are reported in section B.2.6.1 of the CS. The primary and secondary outcomes listed in the CS are described in the published protocol for RM-493-023, accessed by the EAG [9], and are listed in Table 5 of the EAG report. However, of the 14 exploratory outcomes listed in section B.2.3.1 of the CS, none are listed in the published study protocol[9]. In response to EAG clarification question A13 [3], the company states exploratory endpoints were specified in an updated study protocol. However, this update was not provided and the EAG have not been able to access it via other sources (e.g. ClinicalTrials.gov). Therefore, the EAG are unable to confirm whether all outcomes reported in the CS align to those pre-specified in the study protocol, adding uncertainty to the reporting of outcomes.

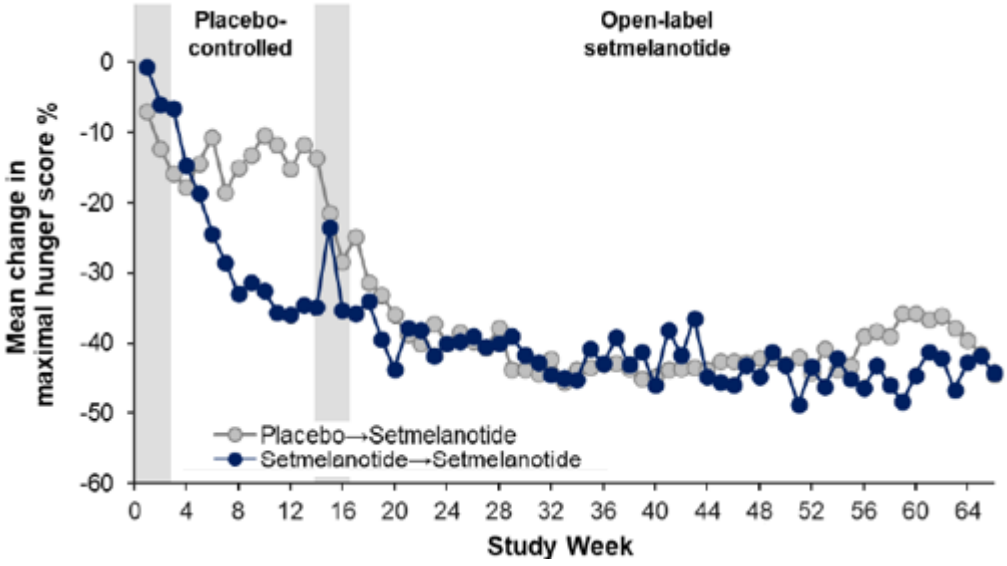
EAG Table 8 presents a summary of the results for the primary and secondary outcomes listed in the CS, and for three exploratory outcomes which informed treatment effect estimates for the economic model. The primary endpoint was the proportion of BBS patients aged ≥12 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks. However, the CS also reports a post hoc subgroup analysis of BBS patients aged ≥18 years. [redacted] of BBS patients aged ≥12 years achieved a ≥10% reduction in body weight from the active-treatment baseline after ~52 weeks of setmelanotide along with 47% of patients aged ≥18 years.

To establish clinical efficacy at 52 weeks, the proportion of BBS patients in study RM-493-023 meeting the primary endpoint were compared against a historical control rate of 10%. This rate was based on an analysis of data from the Clinical Registry Investigating Bardet-

Biedl Syndrome (CRIBBS). The CS asserts that the efficacy of setmelanotide is demonstrated for the primary endpoint (in both ≥12 and ≥18-year-olds). The EAG have not assessed the comparability of participant characteristics between the CRIBBS cohort and RM-493-023 (clarification question A3).

Three pre-specified secondary outcomes assessed hunger scores in participants ≥12 years old (without cognitive impairment). The two outcomes assessed at 52 weeks indicated a reduction in hunger scores, compared to 'active treatment baseline'. The hunger outcome assessed at 14 weeks, was a randomised comparison relative to placebo. A reduction in mean hunger score was observed in the setmelanotide group compared to the placebo group, for most/worst hunger over 24 hours, average hunger over 24 hours, and morning hunger score. However, the EAG note the small sample size and confidence intervals that span zero for five of the six statistical analyses reported in CS Table 24. The EAG note that Figure 6 of the CS (reproduced in Figure 1 below) provides evidence of a placebo effect for hunger score, observable during titration and re-titration periods, and that approximately 10% of the treatment effect may be attributable to this effect, which could be explained as a "regression to the mean" effect. Whilst the 14 week outcomes control for this effect through a randomised comparison, outcomes at 52 weeks do not and so could lead to an over-estimation of effect. The same pattern is seen for BMI-Z / BMI outcomes (company clarification response, reproduced in Figure 5 below).

Figure 1: Mean change in maximal hunger score in patients aged ≥12 years without cognitive impairment (Study RM493023, pivotal patients with BBS) Reproduced from CS, Figure 6.



Grey bars indicate titration and re-titration periods.

As a consequence of the genetic nature of BBS, the CS states that BBS patients have no frame of reference for hunger (clarification question A1). EAG clarification question A12 requested evidence to support the validity of hunger measurement scores used in RM-493-

023, however the company did not directly address this request in their response. Therefore, the EAG question the validity of the three hunger score outcomes reported in the CS as a measure of clinical effectiveness in BBS patients.

The population specified in the final scope is BBS patients with obesity *and* hyperphagia (modified by the company post-marketing approval to focus on severe hyperphagia). Hyperphagia is described as "*a complex condition consisting of an interplay between hunger, satiety and a preoccupation with food*" (CS, B.2.12, Page 107). It is of critical importance to note that hyperphagia was not measured in either RM-493-023 nor RM-493-022 and direct evidence of the impact of setmelanotide treatment on severity of hyperphagia is therefore not available for the EAG to critique. In response to EAG clarification question A1, the company explain that a validated measurement scale for hyperphagia in BBS patients was not available. The EAG concur that there a validated disease-specific scale is not available. In the absence of a validated scale, it is not clear why the Dykens Hyperphagia Scale (developed for Prader-Willi syndrome) was not considered an appropriate proxy. The Prader-Willi syndrome Food Problem Diary (PWFPD) was implemented in RM-493-023 and the CS does not explain why the PWFPD was considered appropriate for a BBS population (caregivers), but the hyperphagia scale was not. The EAG further note that the Food Problem Diary is described as having been derived from the Dykens Hyperphagia Scale in a publication from study RM-493-014 (Haws *et al*, 2020).[10]

Clinical effectiveness results from RM-493-023 that fed into the economic model were derived from post-hoc subgroup analyses analysis for patients aged <18 and ≥18 years of age. Table 8 also reports results from key exploratory outcomes used to inform estimates of the proportion of patients aged ≥18 years who moved from one BMI category to another and the proportion of patients aged <18 years who moved from one BMI Z-score category to another (CS, section B.2.6.1). The EAG also report a risk of bias assessment for this post-hoc outcome, derived for use in the economic model and more detail is provided in 3.2.5.2 of the EAG report.

Key issue 3: How reliable and valid are the clinical effectiveness results for key outcomes reported by RM-493-023?

3.2.5.2 Risk of bias for efficacy outcomes for study RM 493-023

The company assessed Risk of Bias (RoB) for RM-493-023 (CS, Table 20) using the NICE recommended tool[11]. However, this tool considers bias at the study and not outcome-level, and it does not provide an assessment of the overall risk of bias. Additionally, the company assessed RoB using questions intended for RCTs. The EAG consider the outcome data at 52 weeks to be best described as arising from an uncontrolled (single-arm), non-randomised, before-after study and not from a randomized comparison. An appropriate assessment of risk of bias for outcomes at 52 weeks should therefore use a tool for non-randomised studies. The 14-week outcomes (end of period 1) are from a randomised comparison. The EAG consider the Cochrane RoB tool, version 2 (RoB 2)[12] to be the appropriate tool for

randomised studies, as it allows bias assessment at the outcome-level, providing a more robust assessment for technology appraisal.

3.2.5.2.1 End of double-blind randomised study period 1 (RM-493-023; 14 weeks follow-up)

For comparison with the CS assessment, the EAG undertook an independent review across all outcomes at the 14-week endpoint, as this timepoint provides the most robust results for the full randomised cohort. The EAG's full assessment is reported in Appendix 9.1 alongside the CS assessment. Using the NICE recommended tool, the EAG's bias assessments were broadly comparable with the CS, except for:

- The EAG answered 'No' to the question 'Were there any unexpected imbalances in dropouts between groups', as only one participant in placebo group had dropped out at 14 weeks; and
- The EAG answered 'Yes' to the question 'Is there evidence to suggest that the authors measured more outcomes than they reported?', as HRQoL outcomes are not reported in the CS, despite being pre-specified in the published study protocol.[9]

Table 8 Efficacy results for Study RM-493-023 (List of outcomes based on CS, Tables 11 & 17)

Outcome	Comparison	Analysis	Proportion imputed data	Result	EAG comments	EAG risk of bias assessment
Primary outcomes:						
Proportion of patients aged ≥12 years who achieved at least 10% bodyweight reduction from baseline, after 52 weeks.	Single arm, no control group	Pivotal, FAS	Data not provided	Estimated proportion of patients aged ≥12 years achieved a ≥10% reduction in body weight after 52 weeks was [redacted] (n=28) (Table 23 of the CS).	Primary endpoint reported for the full trial population (BBS and AS patients) and BBS patients only. As the submission relates only to use of setmelanotide in BBS patients, results are only reported for BBS population. Not clear how many participants had their outcome value imputed.	Serious[+]
Proportion of patients aged ≥18 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks (post hoc)	Single arm, no control group	Pivotal, FAS	Data not provided	Estimated proportion of patients aged ≥18 years achieved a ≥10% reduction in body weight after 52 weeks was 46.7% (21.3, 73.4) 0.0003 (n=15) (Table 23 of the CS).	Primary endpoint reported for the full trial population (BBS and AS patients) and BBS patients only. As the submission relates only to use of setmelanotide in BBS patients, we present results only for this population. Not clear how many participants had their outcome value imputed.	Serious[+]
Secondary outcomes:						
Mean percent change in body weight from baseline in patients aged ≥12 years after ~52 weeks of treatment.	Single arm, no control group	Pivotal, FAS	Data not provided	Change in bodyweight from 'active-treatment baseline' to 52 weeks was reported in Table 29 of the CS by pivotal patients aged ≥18 years. A reduction from baseline in body weight, compared with a reference value of 0% reduction, was reported with a mean weight loss at 52 weeks of -9.42kg and a mean percent change of -7.57% (n=15).	The prespecified endpoint used an age cut off for patients aged ≥12 years, however the results were reported in the CS using a cut off age of ≥18 years. Not clear how many participants had their outcome value imputed. Percent change in body weight is reported in the Haqq publication [13] in patients aged ≥12 years. However, this includes AS & BBS patients.	Serious[+]
Percent change in daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	Data not provided	Reductions in weekly average percent change from active-treatment baseline to 52 weeks were reported for average hunger over 24 hour (mean [redacted]); most/worst hunger over 24 hours	Clarification response A1 notes that hunger score is not a reliable clinical measure in BBS patients. The EAG notes that hyperphagia was not	Not assessed

				(mean -30.45) and morning hunger (mean [redacted]) in pivotal patients aged ≥12 years without cognitive impairment (n=14).	measured quantitatively or qualitatively in RM-493-023.	
The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	Data not provided	An estimated 57.1% of pivotal patients aged ≥12 years without cognitive impairment (n=14) reached the reduction threshold of ≥25% in weekly average of daily hunger score. When compared to a reference value of 0 it was shown to be statistically significant (p<0.0001, Table 28 of the CS).	Clarification response A1 notes that hunger score is not a reliable clinical measure in BBS patients. The EAG notes that hyperphagia was not measured quantitatively or qualitatively in RM-493-023.	Not assessed
Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment	Randomised, Placebo comparison	All, PCAS	Data not provided	Mean percent change in body weight was described in all patients (pivotal and supplemental) aged ≥18 years. A reduction in body weight from placebo-controlled period baseline to 14 weeks was shown in the setmelanotide treatment arm (n=10), when compared to the placebo arm (n=12). Mean percent change (kg) in the setmelanotide arm after 14 weeks was [redacted] versus [redacted] in the placebo arm [redacted].	The endpoint prespecified in the CS used an age cut off of patients aged ≥12 years, however the outcome was reported using a cut off age of ≥18 years. The Haqq *et al* published study report [13] does report this outcome for patients aged ≥12 years with a mean percent change in the setmelanotide arm of -3.7 (n=18) versus -0.2 in the placebo arm (n=18) (p=0.0019).	Low^
Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment	Randomised, Placebo comparison	All, PCAS	Data not provided	Greater reductions in the weekly average of daily hunger score were observed in the setmelanotide treatment group vs the placebo group from baseline to 14 weeks. Table 24 in the CS provides a summary of the results for most/worst hunger over 24 hours; average hunger over 24 hours and morning hunger.	Outcome reported for patients without cognitive impairment.	Not assessed
Exploratory/post hoc outcomes:						

Proportion of patients aged ≥12 achieving a ≥10% reduction in body weight or ≥15% reduction in BMI after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	Data not provided	Not reported as a composite outcome in CS (≥15% reduction in BMI not reported).	EAG note that this outcome was not reported in the CS. Proportion of patients aged ≥12 achieving a ≥10% reduction in body weight was the primary efficacy outcome.	Not assessed
Change and % change of BMI Z-score in paediatric patients after ~52 weeks of treatment by age group (6-11 years and/or 6-16 years)	Single arm, no control group	Pivotal, FAS	Data not provided	After 52 weeks of setmelanotide treatment a mean change in BMI Z-score of -0.75 points (p=<0.0001) was reported in pivotal patients aged <18 years (n=14, Table 30 in the CS). Mean change over time is shown in Figure 10 of the CS. A 0.2-point reduction from baseline in BMI Z-score was reported in 85.7% of patients aged <18 years (n=14) and 71.4% achieved at least a 0.3-point reduction (n=14, Table 31 in the CS).	Change in BMI Z-score was not reported by 6-11 or 6-16 age groups. But was reported for participants aged <18 years. The rationale for the change is not described.	Serious[+]
Change in BMI after 52 weeks of treatment in patients aged <18 and ≥18 years	Single arm, no control group	Pivotal, FAS	Data not provided	A mean BMI change from active-treatment baseline of -4.22 kg/m2 and a mean percent change of -9.09% was reported in pivotal patients aged ≥18 years (n=12, Table 33 in the CS). A mean BMI change from active-treatment baseline of -3.36 kg/m2 and a mean percent change of -9.50% was reported in pivotal patients aged <18 years (n=14, Table 33 in the CS).	Not explicitly specified as an exploratory outcome in CS.	Serious[+]

[+] Assessed using Cochrane guidance on assessing risk of bias in uncontrolled before-after studies;[14] Assessed using risk of bias tool for RCTs, version 2 ("RoB 2")[12]

Active-treatment baseline = last measurement before the first dose of setmelanotide (i.e. week 0 for setmelanotide group, week 14 for the placebo group). AS = Alström syndrome, BBS = Bardet-Biedl syndrome, BMI = body mass index, CS = company submission, EAG = external assessment group; FAS= full analysis set; RoB = risk of bias.

However, for the 14 week endpoints, the EAG prefer risk of bias assessment using RoB 2 tool[12]. RoB 2 assessments are reported in Table 10 for:

- Mean percentage change in body weight in patients aged ≥12 years (pre-specified secondary outcome)
- Change and percentage change in body weight in patients aged ≥18 years (post hoc outcome)
- Change and percentage change in BMI for all BBS patients (post hoc outcome)

The EAG note mean percentage change in body weight in patients aged ≥12 years was not reported in the CS. Instead, the EAG used the information in trial publication Haqq 2022, appendix p11.[13] Risk of Bias was not assessed for hunger score outcomes, as it is not clear if the measures have been validated and the company response to clarification question A1 indicated that change in hunger score alone was not a reliable measure in BBS patients, due to a lack of a reference point. Health-Related Quality of life (HRQoL) results were not reported in the CS at 14 weeks. Full assessment details are available in Appendix 9.1.1.

3.2.5.2.2 End of single arm, open-label period (study period 2/ 3, ~52 weeks follow-up)

As described above, the company assessed RoB for outcomes at 52 weeks using a tool intended for RCTs. As the 52 week outcomes cannot be considered randomised comparisons, the EAG assessment of risk of bias follows the Cochrane guidance for assessing risk of bias in uncontrolled, before-after studies[14]. EAG assessments are presented in Table 10. The EAG assessed risk of bias for the following clinical effectiveness outcomes, focusing on the primary efficacy outcome for RM-493-023, and the post hoc analyses reported in the CS for patients <18 and ≥18 years old:

- Proportion of BBS patients aged ≥12 years with a ≥10% reduction in body weight from active treatment baseline (primary efficacy endpoint)
- Proportion of BBS patients aged ≥18 years with a ≥10% reduction in body weight from active treatment baseline (subgroup of primary endpoint for purpose of CS)
- Change and percent change in body weight from baseline in patients aged ≥18 years (outcome not specified in CS as either secondary or exploratory)
- Change and percent change in BMI from baseline in patients aged <18 years (outcome not specified in CS as either secondary or exploratory)
- Change and percent change in BMI from baseline in patients aged ≥18 years (outcome not specified in CS as either secondary or exploratory)
- Change in BMI Z-score from baseline in patients aged <18 (outcome not specified in CS as either secondary or exploratory)
- Proportions of patients aged <18 years achieving at least 0.2 point reduction in BMI Z-score from baseline (not specified in CS as either secondary or exploratory, informs economic model)
- Proportions of patients aged <18 years achieving at least 0.3 point reduction in BMI Z-score from baseline (not specified in CS as either secondary or exploratory, informs economic model)

- BMI shift data for individual patients aged ≥18 years who were classified as 52week responders (post-hoc analysis, used in economic model)
- BMI Z-score shift data for individual patients aged <18 years who were classified as 52week responders (post-hoc analysis, used in economic model)

Overall risk of bias was judged to be serious for all ten outcomes. Risk of bias due to confounding was judged to be moderate for all outcomes. Risk of bias due to selection of participants into the study, deviations from intended interventions and outcome measurement were judged to be low for all outcomes. The missing data domain was judged to be at serious risk of bias for all outcomes, due to the unreported, yet potentially significant, proportion of imputed missing outcome data at 52 weeks and concerns that the missingness could potentially be related to the values of the missing outcomes. The EAG notes that multiple imputation does not eliminate bias that arises due to missing data (See EAG, section 3.2.5.1).

The EAG rated the risk of bias due to selective reporting as low for the primary efficacy outcome (proportion of BBS patients aged ≥12 years with a ≥10% reduction in body weight from active treatment baseline) as this outcome was clearly pre-specified in the design paper.[9] The remaining nine outcomes, were judged to be at serious risk of bias due to selective reporting, due to concerns that specific results could have been selected for reporting, based on the value of the estimates, from potentially multiple analyses for age-subgroups, that differed from those pre-specified. Outcomes were presented with different age-groups compared with what was listed in the CS as pre-specified. The full study protocol was not available to determine whether each assessed outcome differed from those that were pre-specified.

Key issue 4: What is the impact of potential bias arising from absence of randomised, controlled comparisons for key clinical outcomes at 52 weeks follow-up in RM-493-023?

Table 9: Risk of Bias in RM-493-23 trial, assessed by EAG for weight and BMI change outcomes at 14 weeks.

Outcome-level risk of bias assessment for weight and BMI change outcomes at 14 weeks using the Cochrane RoB 2 tool[12]			
Bias domain	Outcomes		
	Change and % change in body weight from baseline to 14 weeks in 32 BBS patients aged ≥18 years (CS Table 25)	Change and % change in BMI from baseline to week 14 for all 44 BBS patients (CS Table 26)	**Planned secondary efficacy endpoint**: Mean % change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment: –2·1% (95% CI −4·6% to 0·4%; p=0·052; Haqq et al. appendix p 11)."[13]
Randomisation process	Low risk	Low risk	Low risk
Deviations from intended interventions	Low risk	Low risk	Low risk
Missing Outcome Data	Low risk	Low risk	Low risk
Measurement of the outcome	Low risk	Low risk	Low risk
Selection of the reported result	Low risk	Low risk	Low risk
Overall risk of bias judgment	**Low risk**	**Low risk**	**Low risk**

BBS=Bardet-Biedl syndrome, BMI=Body Mass Index; CI = confidence interval; CS = company submission; EAG = External Assessment Group; "RoB 2" = Abbreviated name of the Cochrane Risk of Bias tool, version 2.

Table 10: Risk of Bias in RM-493-23 open-label single-arm continuation study, for endpoints at 52 weeks, assessed by EAG for primary efficacy outcome; weight, BMI and BMI-z change from baseline; and post hoc outcomes used in the economic model.

	Risk of bias domains						**Overall risk of bias for the outcome**
Outcomes	Confounding	Selection of participants into the study	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	
Primary efficacy endpoints:							
Proportion of BBS patients aged ≥12 years with a ≥10% reduction in body weight from active treatment baseline to 52 weeks setmelanotide treatment (pivotal FAS, CS Table 23, N=28)	Moderate	Low	Low	Serious	Low	Low*	**Serious**
	Confounding (applies to all listed outcomes): Moderate concerns for confounding due to lack of any control for confounding, but the differences in groups in weight reduction in the placebo-controlled period and in the later open-label period are somewhat reassuring. **Missing data** (applies to all listed outcomes): Major concerns about missing outcome data at 52 weeks, which have been imputed, and missingness could be related to the values of the missing outcomes. Multiple imputation methods are unlikely to eliminate bias due to missing data. ***Selective reporting:** Full protocol not available. However, this outcome is listed a pre-specified primary endpoint in the published design paper [9] in the CS and the company trial [13], hence no concerns for this outcome.						
Subgroup: Proportion of BBS patients aged ≥18 years with a ≥10% reduction in body weight from active treatment baseline to 52 weeks setmelanotide treatment (pivotal FAS, CS Table 23, N=18)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Full protocol not available. Concerns that specific results could have been selected for reporting, based on the value of the estimates, from multiple analyses by age-subgroups that differed from those pre-specified.						
Weight, BMI and BMI-z change from baseline:							
Change and % change in body weight from baseline to 52 weeks setmelanotide treatment in Patients aged ≥18 years (pivotal FAS, CS Table 29, Figure 9, N=15)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Full protocol not available. Concerns that specific results could have been selected for reporting, based on the value of the estimates, from multiple analyses by age-subgroups that differed from those pre-specified.						
Change and % change in BMI from baseline to 52 weeks of setmelanotide treatment in patients aged	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above.						

<18 and ≥18 years (pivotal FAS, CS Table 33, N=16 and 15 respectively)	**Missing data**: as for primary endpoint, see above. **Selective reporting:** Full protocol not available. Concerns that specific results could have been selected for reporting, based on the value of the estimates, from multiple analyses by age-subgroups that differed from those pre-specified.						
Change in BMI Z-score from baseline to 52 weeks of setmelanotide treatment in patients aged <18 and years (pivotal FAS, CS Table 30, N=16)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Full protocol not available. Concerns that specific results could have been selected for reporting, based on the value of the estimates, from multiple analyses by age-subgroups that differed from those pre-specified.						
Outcomes informing the economic model:							
Proportions of patients aged <18 years achieving at least 0.2 and 0.3 point reduction in BMI Z-score from baseline after 52 weeks of setmelanotide treatment (pivotal FAS, CS Table 31, N=14 for both outcomes)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Full protocol not available. Concerns that specific results could have been selected for reporting, based on the value of the estimates, from multiple analyses based on outcome dichotomization, and age-subgroups that differed from those pre-specified.						
Post-hoc analysis: BMI shift data for individual patients aged ≥18 years who were classified as 52week responders (pivotal patients, CS Table 34, N=7; average responder shift was [redacted] BMI class)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Same risk of bias concerns as for the BMI change outcome from which this outcome is derived, with some additional concerns as this is a post-hoc analysis in the responders only subgroup. However, this may be appropriate for use in the economic model.						
Post-hoc analysis: BMI Z-score shift data for individual patients aged <18 years who were classified as 52week responders (pivotal patients, CS Table 35, N=12, average responder shift was [redacted] BMI Z-score class)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: as for primary endpoint, see above. **Selective reporting:** Same risk of bias concerns as for the BMI-Z score change outcome from which this outcome is derived, with some additional concerns as this is a post-hoc analysis in the responders only subgroup. However, this may be appropriate for use in the economic model.						

BBS=Bardet-Biedl syndrome, BMI=Body Mass Index, CS = company submission, EAG = External Assessment Group, FAS=full analysis set (as defined in company submission).

3.2.5.3 Efficacy outcomes for study RM-493-022

Only setmelanotide responders were eligible to take part in RM-493-022. Responders were defined as *"patients aged ≥18 years achieving ≥10% weight reduction or patients aged <18 years achieving a ≥0.3 BMI Z-score reduction after 1 year of setmelanotide treatment in their index trial*" (CS, page 106). The EAG note that a different definition of response is used in the cost effectiveness analysis in the CS (EAG, section 4.2.6.1). The primary outcome in RM-493-022 was safety and tolerability of setmelanotide, assessed by the frequency and severity of adverse events (AEs); changes in physical examination, electrocardiogram (ECG), vital sign, and laboratory evaluations; and the occurrence of injection site reactions. None of these outcomes appear to inform the economic model, however section 2.6.2 of the CS states that they do feed into the model.

The clinical effectiveness results for RM 493-022 are reported in section B.2.6.2 of the CS[2] and address BMI, BMI Z-score, body weight, and weight related results beyond 3 years of treatment. There were no prespecified secondary outcomes for RM 493-022. Eight exploratory outcomes are listed in section B.2.3.1 of the CS. As with RM-493-023, the company stated that these outcomes were pre-specified in a study protocol, which the EAG has been unable to access. In section B.2.6.2 of the CS the company state that results for "*Maintenance of effect among patients who initially responded to setmelanotide treatment*" was used in the economic model. However, the EAG highlights this is as another potential inconsistency between what is stated in the CS and what was executed in the economic model. No outcomes from RM-493-022 explicitly feed into the model, as reported in the CS.

Results in section B.2.6.2 of the CS, describe total time on setmelanotide treatment, not time in study RM-493-022. Decrease in BMI was maintained (all age groups), with a mean percent change of [redacted] reported at month 36 [redacted]. Table 44 in the CS shows mean BMI change in responders at 12, 18, 24 and 36 months. [redacted] patients ([redacted]) at month 12 had maintained ≥10% weight reduction from their index trial baselines and [redacted] patients ([redacted]) at month 36. The company noted the decrease in numbers seen at the 36-month timepoint and assert this was due to a proportion of patients not having completed 36 months of treatment at the time of data reporting.

Changes in body weight from baseline and 52 weeks was reported at 12, 18, 24 and 36 months in adults only [redacted] (Table 45, CS). The company deemed reporting of body weight for paediatric patients was not appropriate as this population is still growing and therefore be increasing in body weight over time. Therefore, paediatric patients were omitted in the data reporting. The mean percent change in body weight at 36 months was [redacted], however this only included [redacted] adult patients as only [redacted] had received 36 months of setmelanotide treatment, at time of reporting. Due to the small sample size, the EAG notes the large amount of uncertainty regarding the treatment effect on body weight.

The company noted BMI Z-scores to be a more appropriate way to characterise obesity in this population than change in body weight. BMI Z-scores were reported separately in the

CS for paediatric responders at 12, 18, 24 and 39 months (Table 46, CS). The mean change in BMI Z-score in responders at 36 months [redacted] was [redacted] patients [redacted] at month 12 had maintained ≥0.3 BMI Z-score reduction from their index trial baselines and [redacted] patients [redacted] at month 36.

3.2.5.4 Risk of Bias assessment for Study RM 493-022

The company assessed RoB for RM-493-22 using the NICE recommended, study-level tool for non-randomised studies (CS, Table 21).[11] Since no outcomes from RM-493-22 were reported as key clinical effectiveness endpoints, nor used to inform the economic model, the EAG have not carried out an independent review using the same tool, or an assessment based on the non-randomised study guidance recommended in the Cochrane Handbook.[14]

3.2.6 Health related quality of life outcomes from RM-493-023 and RM-493-022

Findings for Health-related quality of life (HRQoL) are presented in section B.2.6.1.5 in the CS [2], for the pivotal cohort only after ~52 weeks of treatment. HRQoL after 14 weeks of treatment was listed as an exploratory endpoint in the CS, however no results are reported in the CS. In RM-493-023, self-reported HRQoL was measured using the validated Paediatric Quality of Life Inventory (PedsQL), the validated Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite) and EQ-5D-5L actual scores. HRQoL data from RM-493-023 were also published in a separate paper by Forsythe *et al* [1]. Table 11 summarises results reported in the CS and Forsythe paper and highlights discrepancies. These discrepancies introduce confusion to the interpretation of the HRQoL results, however they do not impact the cost-effectiveness results as trial-based HRQoL assessment do not feed into the current economic model. HRQoL is discussed further in section 4.2.7 of the EAG report.

Table 11 HRQoL data for Study RM-493-023 at 52 weeks

	CS	Forsythe 2023[1]	EAG Comments
IWQOL-Lite (all patients ≥18 years)	NR	Baseline score = 74.9 Mean improvement = +12 points **(N = 11)**	Outcome not reported in CS for all patients.
IWQOL-Lite (patients ≥18 years without cognitive impairment)	Baseline score = 74.9 Mean improvement = +12 points **(N = 11)**	Baseline score = 70.7 Mean improvement = +12 points **(N = 7)**	Inconsistent reporting of results between CS and Forsythe 2023 [1]. Note that results in the CS for 'without cognitive impairment' are numerically the same as Forsythe 2021 & 2023 [1 15] results for 'All patients'.
PedsQL (all patients <18 years)	NR	Baseline score = 67.2 Mean improvement = +11.2 points **(N = 9)**	Outcome not reported in CS for all patients.
PedsQL (patients <18 without cognitive impairment)	Baseline score = 67.2 Mean improvement = +11.2 points **(N = 9)**	Baseline score = 83.3 Mean improvement = +3.3 points **(N = 3)**	Inconsistent reporting of results between CS and Forsythe 2023. Note that results in the CS for 'without cognitive impairment' are the same as Forsythe 2021 & 2023 [1 15] results for 'All patients'.

CS = company submission, NR = not reported

The CS detailed self-reported HRQoL was assessed using the validated IWQOL-Lite for patients aged ≥18 years and the validated PedsQL for patients aged <18 years. The EAG note that no references were provided by the company to support the validation of PedsQL in a BBS population.. Additionally, the EAG notes that HRQoL data was not reported for carers in either RM-493-023 or RM-493-022, as included in the NICE and company scope, which limits information available to model the disutility of carers for the economic model. Functional health and well-being were measured in both RM-493-023 and RM-493-022 using the SF-36 and SF-10 health survey for children. It is not clear if these scales have been validated for use in a BBS population. These measures were listed in the CS as exploratory for both studies and no results were reported for these outcomes for either study.

EQ-5D-5L data is only reported in the CS for RM-493-023 and not in Forsythe.[1] Across the 5 subscales assessed (Table 41, CS), mean baseline EQ-5D-5L scores ranged from [redacted] in pivotal cohort participants aged ≥16 years without cognitive impairment (n=13). After 52 weeks of setmelanotide treatment, participants reported improvements (decreases) in mobility scores [redacted] usual activities scores [redacted] and anxiety/depression scores [redacted]

Key Issue 5: To what extent does the selective outcome reporting of exploratory outcomes reduce confidence in clinical effectiveness and cost-effectiveness results?

3.2.7 Safety analyses for RM-493-023 and RM-493-022

Adverse events (AEs) for RM-493-023 and RM-492-022 were reported in Section B.2.10 in the CS.[2] In RM-493-023, AEs were monitored throughout the study and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [9]. All 44 BBS patients experienced at least 1 treatment-emergent adverse event (TEAE) (Table 50, pg103 CS). Three patients experienced a serious adverse event (SAE), which was considered not to be setmelanotide related. During the double-blind placebo-controlled period, skin hyperpigmentation and vomiting were only reported as a TEAE in the setmelanotide group. Other TEAEs reported were similar across the two arms. TEAEs let to study drug withdrawal in 3 patients, 2 of which were from the placebo group during the placebo-controlled period.

All 30 BBS patients in RM-493-022 experienced at least 1 TEAE during treatment with setmelanotide, in both the index trial and Study RM-493-022. [redacted]. The most common TEAEs listed were injection reactions, skin hyperpigmentation and nausea (Table 52, pg104 CS). Post clarification request (B19), the data from RM-493-023 for nausea, vomiting and injection site reaction outcomes were included in the economic analysis (BBS and AS participants).

3.2.8 Subgroup analyses

The primary outcome specified for RM-493-023 was based on an age threshold of ≥12 years of age. However, the NICE scope required an age dichotomisation of <18 and ≥18 years of age (corresponding to paediatric and adult populations), and the analyses reported in the CS for RM-493-023 and RM-493-022 should be considered as post hoc subgroup analyses.

Section B.2.7 and Appendix E of the CS reports planned subgroup analysis by cognitive status on reduction in body weight, BMI and hunger using data from RM-493-023 [2], [16]. 'Statistically significant' reductions were observed in body weight (Table 1, Appendix E) and BMI (Table 3, Appendix E) from baseline to 52 weeks in pivotal patients aged ≥18 years irrespective of cognitive status. Reductions in BMI Z-scores (Table 2, Appendix E) from baseline to 52 weeks were also observed in pivotal patients aged <18 years irrespective of cognitive status. The company noted the small sample size for this group (n=4).

Hunger in patients with cognitive impairment (of all ages) was measured using the Prader-Willi Syndrome Food Problem Diary (PWS-FPD), completed by the caregiver. Reduction in mean hunger scores were reported from baseline to 52 weeks (Table 4, Appendix E).

3.2.9 Protocol deviations

The CS notes that protocol amendments were made during study RM-493-023. The timing of the protocol amendment is not explicitly stated in the CS, however it appears to have been before recruitment of the supplemental cohort. It is not clear if the results from the pivotal cohort were available at the time of the protocol variation. A summary of protocol amendments for RM-493-023 is reported in the supplementary appendices of the published main study report [13]. Two key amendments for critique are:

- Given the rarity of BBS (and AS), a supplemental cohort of patients were enrolled to increase sample size of the study. Patients from this cohort were randomised to placebo or setmelanotide for a 14-week double-blind period and then treated with open-label setmelanotide, following the same protocol as the pivotal cohort. However, supplemental participants were permitted to enrol in the extension study (RM-493-022) at 24 weeks and were considered to have completed the study at that time point. The potential impact of this variation on the validity of results is discussed in 3.2.5 and 3.2.5.2.2.
- Use of GLP-1 receptor agonists and anorectic agents or drugs were permitted. In answer to clarification question A8 [3], the company stated [redacted] As such, the EAG considers this would not have impacted the validity of the results. Additionally, the EAG's clinical advisors agreed that the inclusion of participants who had stabilised weight loss on GLP-1 receptor agonists was reasonable.

3.3 Critique of the systematic literature review

The Company report a systematic review of clinical effectiveness to synthesise the evidence from clinical trials or observational studies. The EAG identified concerns in the conduct and completeness of the review following a critique using the ROBIS tool[17] (see Appendix 9.2). There are two key concerns that are described in more detail below:

- The searches missed eligible two key published study reports (see 3.3.1).
- The approach to data extraction is unclear (see 3.3.2).

3.3.1 The SLR searches missed eligible published study reports.

Although the CS includes all eligible studies, the EAG note that two key study reports and published conference abstract are missing from the SLR as they were published after the date of last search (Last search August 2022). These studies are:

1. The main published trial report for RM-493-023 (published in November 2022)[13];
2. The main publication of HRQoL data for RM-493-023 (published January 2023)[1]; and
3. A published conference abstract of long-term extension data for RM-493-022.[18]

The company acknowledges the publication of the first journal article as an addendum in the systematic review. However, it is unclear if the journal article was included in the systematic review and assessed alongside other eligible studies. No information is included for the second and third publication, which may have been 'in press' at the time of the CS. The company could have included in-submission or pre-publication (unpublished) versions of these study reports in their SLR. Alternatively, update searches could have been conducted and would have identified publications had they been repeated in February 2023.

3.3.2 The approach to data extraction is unclear.

The company prioritised the most recent full-text publications for data extraction. Best practice guidance is to extract all study reports, irrespective of publication type or date of publication. The CS does not report the process for data extraction (i.e., it is not clear if data extraction was second checked). As a minimum, we would expect data extraction be checked to identify any errors. The EAG have noted data discrepancies between the CS and the key trial journal publications (e.g. section 3.2.5). As full-text publications are missing from their review, this raises additional concerns about the completeness of data extraction. Accordingly, the EAG have some concerns about the suitability of the company's systematic review to appropriately and correctly summarise the evidence relied upon in this submission.

3.4 Conclusions of the clinical effectiveness section

The company's submitted evidence is broadly in line with the final scope. However, the specified population is narrower and focuses on a subgroup of BBS patients with severe hyperphagia. The company state it appropriate to restrict the CS to this subgroup due to the cost-effectiveness and clinical benefit of setmelanotide in these patients. However, this is based on an assumption that all 'responders' from the main study (RM-493-023) had severe hyperphagia at baseline. This assumption cannot be verified, as hyperphagia was not measured in RM-493-023 and nor was it an eligibility criterion for entry to the study. The company argues that there is no validated scale with which hyperphagia can be assessed in BBS patients. As such, it is not clear how clinicians will be able to identify patients with severe hyperphagia in practice and the EAG considers that setmelanotide is likely to be

prescribed to a wider population of BBS patients with obesity than the narrow (post hoc) subgroup proposed in the CS.

There is some doubt as to whether ongoing management for patients administered setmelanotide would take place within primary care, as claimed by the CS. EAG clinical advice considered it more likely that this would take place in a local, secondary care setting with support from the BBS specialist centres. Clinical advisors agreed with the CS positioning of setmelanotide as an addition to current best practice and not a replacement. Clinical advice supported the CS assertion that dietary and lifestyle advice was current practice in England and that bariatric surgery was probably not appropriate in a BBS population.

3.4.1 Is there evidence of clinical effectiveness?

The estimates of clinical effectiveness in the CS come from the main study RM-493-023, and the extension study RM-493-022. Weight and hunger outcomes measured at the end of the randomised comparison (at 14 weeks) are the most robust and reliable results available from RM-493-23 and provide evidence of clinical effectiveness. However, 14-week data are not used in the economic model and were not considered as key effectiveness outcomes in the CS. There is evidence of clinical effectiveness after 52-weeks of setmelanotide for prespecified primary and secondary weight and hunger outcomes. However, this evidence is considered at serious risk of bias as it arises from a single arm, uncontrolled before-after study period and results are less reliable for establishing causal effects. Despite the focus of the appraisal on the importance of reducing hyperphagia as a means to reducing obesity in BBS patients, hyperphagia was not measured as an outcome in the CS or underlying clinical studies. Consequently, there is no direct evidence that setmelanotide reduces severity of hyperphagia, as is claimed by the CS.

Clinical effectiveness results from RM-493-023 that fed into the economic model were derived from post-hoc subgroup analyses for participants aged <18 and ⩾18 years old, who were classified as 'responders' at 52 weeks. This analysis was based on N=7 participants in the ≥18 years old subgroup and N=12 in the <18 years old subgroup. Outcomes that fed into the model assessed the proportion of patients aged ≥18 years who moved from one BMI category to another and the proportion of patients aged <18 years who moved from one BMI Z-score category to another. They are also considered at serious risk of bias, based on the underlying outcomes from which they are derived, with some additional concerns as this is a post-hoc analysis in the responders only subgroup.

Due to the small number of participants from the UK (N=2) in the studies informing the CS, the generalisability of the clinical effectiveness evidence to the NHS is not clear.

3.4.2 Uncertainties regarding the clinical effectiveness data

There are unresolved concerns regarding selective outcome reporting. The EAG are unable to confirm whether all outcomes reported in the CS align to those pre-specified in the updated (unpublished) study protocol for RM-493-023 or RM-493-022, as neither are

available. Although data are available and published in Forsythe *et al* [1], the CS provides limited information on HRQoL outcomes. Inconsistencies in reporting between Forsythe *et al* [1] and the CS have been noted.

There are also reporting inconsistencies noted within the CS. Table 11 lists over 20 study outcomes RM-493-023 that are "used in the economic model". However, sections B.2.1 and B.3.3.2 of the CS states that only baseline characteristics and (post hoc) BMI/BMI-Z score shift outcomes directly inform the model. A similar inconsistency is noted for multiple imputation, generating uncertainty about the extent of imputed data for the key clinical effectiveness outcomes reported in the CS. Due to the small sample sizes involved – especially for the post hoc subgroup analyses informing the economic model – the absence of information on the number of participants with imputed endpoint data is of especial concern and increases the uncertainty in the robustness and generalisability of clinical effectiveness estimates. The validity of multiple imputation relies on there being a sufficient number of participants with a full set of measurements across all outcomes and covariates of interest. However, it should be noted that, even a valid multiple imputation approach does not eliminate bias arising due to missing data.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The Company report a systematic review of cost-effectiveness to synthesise the evidence on costs and resource use. The scope of the review broadly aligns with the decision problem for the appraisal, as reported in Table 3.

The systematic review did not identify any eligible studies for review (CS Section B.3.1). The EAG undertook scoping searches and confirmed this finding. Of relevance, however, is NICE HST21 for setmelanotide in patients with obesity caused by leptin receptor (LEPR) or Proopiomelanocortin (POMC) deficiency.[19] The company's approach to deriving inputs to their model largely follows the approach taken for NICE HST21. [19]

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 12 provides the EAGs comments on how the companies model adheres to the NICE reference case.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with the NICE reference case. Disutilities included for care-givers
Perspective on costs	NHS and PSS	Consistent with the NICE reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Consistent with the NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with the NICE reference case, however does assume that the benefits of setmelanotide persist into the long-term without any waning of effect.
Synthesis of evidence on health effects	Based on systematic review	EAG agree evidence synthesis not possible due to no other studies identified in the systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects are expressed in QALYs.

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The companys approach does not follow the hierarchy of preferred HRQoL methods as per NICE reference case.[11] Despite having Health-related quality of life (HRQoL) available for children and adult BBS patients in RM-493-023,[1] the company relied solely on HRQoL data for children and adults with obesity from external sources (Riazi 2010[20] and Alsumali 2018[21]). No review of evidence was performed to support the choice of these external sources.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Riazi 2010[20] reported PedsQL scores for children with obesity which were mapped onto EQ-5D utility scores using Khan's 2010[22] algorithm. The same algorithm could have been applied to PedsQL scores for the trial paediatric BBS patients. The vignette study to capture hyperphagia was performed according to DSU methodology. However, in a study sponsored by the company (Forsythe 2023[1]), changes in PedsQL scores for BBS patients on Setmelatonide were reported as clinically significant. The changes in PedsQL scores reported should capture the health benefits of decreased hyperphagia and were not used in the model. The EAG prefers preference data from mapped PedsQL scores in the BBS population over applying a multiplier obtained from a vignette study to mapped PedsQL scores in a different obese/overweight population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with the NICE reference case. Carer disutility included.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued	Consistent with the NICE reference case. No PSS costs identified. The EAG requested that costs were updated to current prices, which the company did in

	using the prices relevant to the NHS and PSS	their updated model following clarification questions. The CS assumes monitoring resource use and costs will be supported in primary care, whereas the EAG's clinical advisors suggest these will take place in secondary/tertiary care.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with the NICE reference case in their base case.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

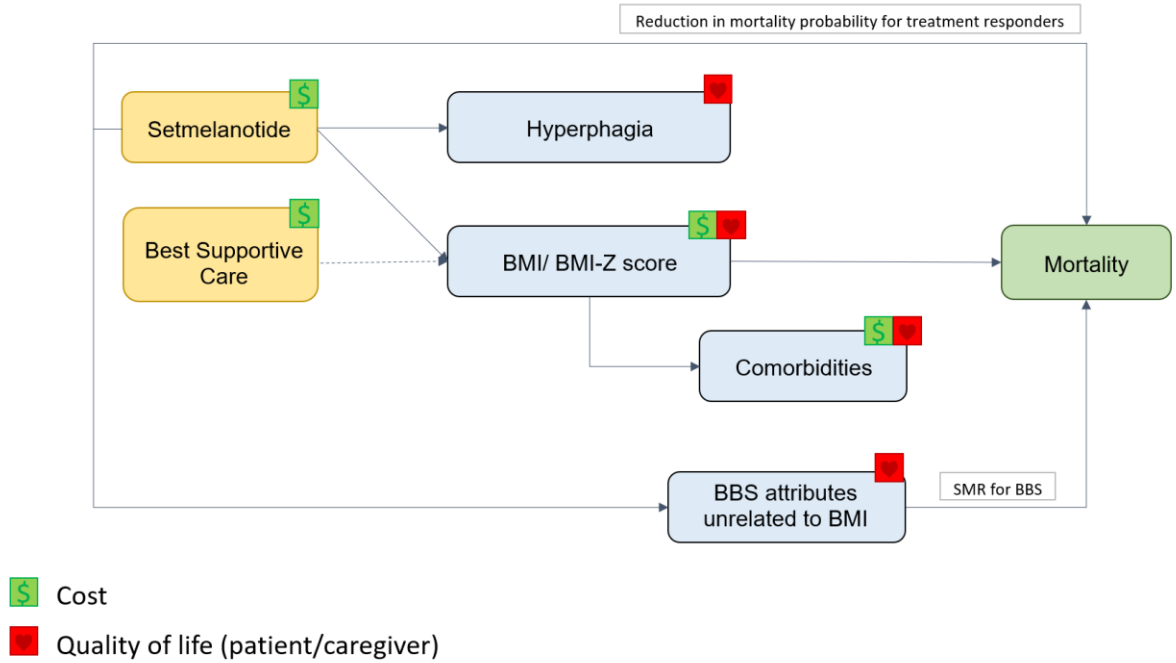
4.2.2 Model structure

The CS model addresses the decision problem described in Table 3 using a lifetime cohort model built in Microsoft Excel with annual cycles, based on UK life tables, illustrated in Figure 2, and described in full in CS section B.3.3.2.

Patients are categorised according to their BMI-Z score (paediatrics) or BMI score (adults) and hyperphagia state. Patients on Best Supportive Care (BSC) are assumed to remain in the same BMI-Z / BMI class and remain in the severe hyperphagia state. Patients on setmelanotide are categorised according to their response to treatment. Those who do not respond are assumed to stop treatment at 14 weeks and remain in the same BMI-Z / BMI class and remain in the severe hyperphagia state (as for BSC). Patients who respond to treatment at 14 weeks remain on treatment until they discontinue. Responders are assumed to move to the mild hyperphagia state and move to a lower BMI-Z / BMI class, and they remain in these states long-term until they discontinue setmelanotide. A small proportion of patients discontinue treatment each year and return to their initial BMI-Z / BMI class and the severe hyperphagia state. When paediatrics become adults their BMI-Z class is mapped to an adult BMI class (CS Table 53). BMI/BMI-Z categories differ in costs and HRQoL. Costs and QALYs are also accrued via comorbidities which depend on age and BMI-Z / BMI class and are associated with costs and utility decrements. Hyperphagia states are associated with different HRQoL, which is applied as a multiplier of the overall utilities and is assumed to be independent of BMI-Z / BMI states. Carer disutilities are included in the model for both paediatrics (1.5 carers) and adults (1 carer).

Mortality is modelled using UK life-tables multiplied by a Standardised Mortality Rate (SMR) by BMI-Z / BMI class, and a further SMR for BBS patients compared to the general population. In the original submission a further multiplicative SMR was applied to represent benefits of setmelanotide in reducing onset of non-BMI related comorbidities, however this was set to 1 in the company's updated model following clarification questions.

Figure 2 Schematic representation of how costs and QALYs accrue in the company's model (Reproduced from CS Figure 12)



The EAG considers a life-table approach to modelling the impact of obesity-related comorbidities on mortality and health-related quality of life to be appropriate. However, the model makes some strong assumptions that may lack validity. The assumption that all patients who respond to treatment move from the severe to the mild hyperphagia state is likely to be an over-simplification, and some patients may be expected to move to a moderate hyperphagia state. Furthermore we would expect that this would be linked to BMI-Z / BMI class, with patients who have a bigger response on hyperphagia also having a bigger response on BMI-Z / BMI class. However these are assumed to be independent in the model.

Key Issue 6: All responders are assumed to move to the mild hyperphagia state, independent of change in BMI-Z / BMI.

The model assumes that reductions in BMI-Z / BMI class would be fixed and maintained over a patients lifetime whilst they are taking setmelanotide. Whilst there is no long-term evidence available for setmelanotide, our clinical advisors expected there may be some waning of effect based on longer-term evidence for GLP-1 receptor agonists [23]. See section 4.2.6.2 below.

We consider it appropriate to model the prevalence of co-morbidities by age and BMI-Z / BMI class, although some of the costs and disutilities may already be captured in the costs and utilities associated with BMI-Z / BMI categories. We also consider it appropriate to include carer disutilities.

We heard that it was unlikely that setmelanotide would have additional mortality benefits apart from those related to changes in BMI-Z / BMI. After clarification questions, the company set the non-obesity related SMR to 1, which the EAG considers appropriate.

4.2.3 Population

The CS base case analysis assumes a population of paediatric patients (starting age 6 years, 50% female) with BBS who have severe hyperphagia and obesity. A subgroup analysis was conducted for an adult population, and an additional subgroup analysis for a mixed population of 60% paediatric patients and 40% adult patients. The distribution of initial BMI/BMI-Z categories were taken from Study RM 493-023, pivotal patient SAS presented in (Table 13 of CS).

In response to clarification question B1 the company states that setmelanotide will be initiated in one of the four existing specialist clinics for the management of BBS, and clinicians will base their decision to prescribe setmelanotide on the patient's weight trajectory, and on the extent to which eating behaviours in Table 13 are interfering with their ability to carry out their daily life, which their clinical experts felt were reflective of their patients who are most severely affected by hyperphagia.

Table 13 Description of severe hyperphagia provided by the company in response to clarification B1

Severe hyperphagia description	
Subjective Experience	• You **almost never feel full** after a **normally sized meal** • You become **hungry again almost immediately** after eating a meal • Thinking about food **almost always interferes** with your **normal activities** of daily living
Observable Behaviors	• You overeat to the point of **discomfort at most meals** • You eat **almost constantly** • You eat during the **hour** before you go to bed **almost every night** • You **eat** a large number of calories when you wake up **during the night almost every night** • You try to **sneak food** without people knowing **almost every day**
Impact	• You become **extremely distressed or upset** when **denied food** • Because of hunger and eating behavior, you have **severe problems performing daily activities** such as self-care, getting around, leisure activities and work or school • Because of hunger and eating behavior, you have **severe problems with your relationships** with family and friends

The modelled population in the CS is narrower than the license and the NICE scope because it only includes BBS patients with severe hyperphagia. Our clinical advisors told us that BMI-Z / BMI together with a clinical impression of severe hyperphagia would be the main criteria

used to consider treatment with setmelanotide in BBS patients (see section 2.2). However, the population for whom setmelanotide is used could be broader than that modelled by the company (see Key Issue 1). In response to clarification question B2 the company states that approximately 60% of children with BBS have severe hyperphagia based on the description in Table 13, and that they expect a similar proportion for adult patients. We therefore explore a scenario where 60% of patients have severe hyperphagia initially, and 40% have moderate hyperphagia.

We heard from our clinical advisors that although more BBS patients are being diagnosed in childhood, it would be a long time before all patients were diagnosed as children, and so it seems appropriate to include adults in a scenario. Given the uncertainty around the split between adults and children (and that this is likely to change over time) we prefer to interpret the results separately for adults and children as 2 subgroups, rather than as a mixed population.

We noted that in the CS model the age at which patients move from paediatrics to adults was either 18 or 19 years old, applied inconsistently. The company corrected this to 18 in their response to clarification question B8 , which had a minimal impact on the ICER increasing it from £191,759 to £192,572

4.2.4 Interventions and comparators

There is a single comparator, Best Supportive Care (BSC), comprising lifestyle, dietary interventions and behavioural therapy, as described in NICE guideline CG189. [24] The company states that the interventions comprising BSC are ineffective treatments for BBS patients because they do not address hyperphagia. Setmelanotide is a selective melanocortin-4 receptor agonist which is expected to be used in addition to BSC.

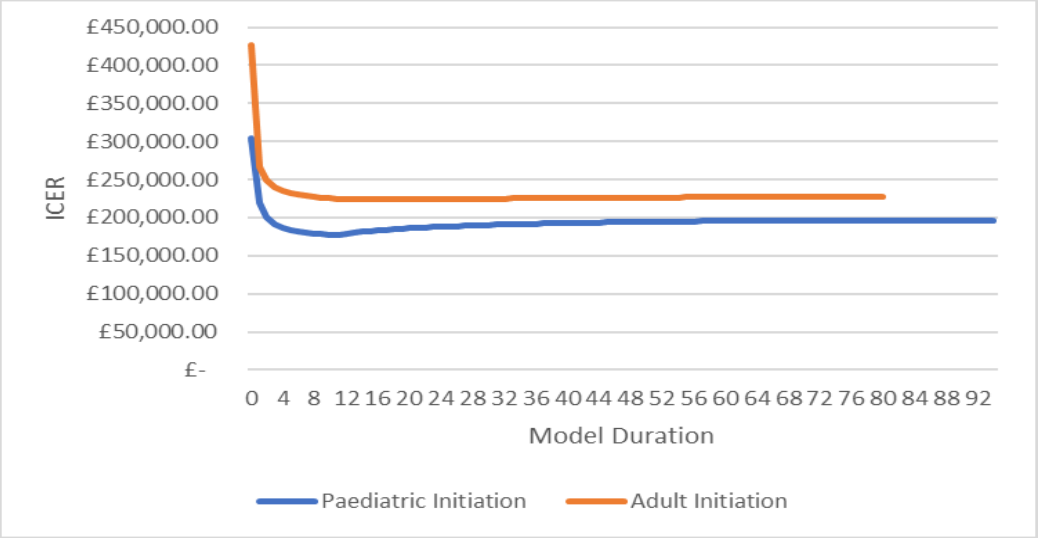
We heard from our clinical experts that bariatric surgery is not usually suitable for this patient population, and so the EAG is content that this is excluded as a comparator. The GLP-1 receptor agonist Semaglutide has recently (during this review) received a positive recommendation to treat obesity in adults in TA875 (https://www.nice.org.uk/guidance/TA875), but this is not available for children. GLP-1 receptor agonists act on hunger, and so have the potential to be beneficial to BBS patients. The EAG consider that going forwards semaglutide has become a relevant comparator for the adult BBS population. However, we acknowledge that this is a very recent development.

4.2.5 Perspective, time horizon and discounting

A National Health Service and Personal Social Services (NHS PSS) is taken with costs and outcomes discounted at an annual rate of 3.5% in line with the NICE reference case. The CS model is a lifetime time horizon which is appropriate to capture the differences in costs and outcomes between setmelanotide plus BSC compared with BSC alone.

The EAG does however have some concerns about the extrapolation of treatment benefits on both hyperphagia and BMI-Z / BMI into the long-term in the absence of any long-term data. To explore the impact of the uncertainty in the extrapolation the company provided Figure 3 (in response to clarification question B5) which shows that the ICER stabilises beyond 2 years. The ICER from the company's base-case model is not sensitive to the time-horizon, however it is sensitive to assumptions about treatment waning, as we discuss below in section 4.2.6 and explore in scenario analyses.

Figure 3 Companys base-case ICERs by time horizons (model duration)



4.2.6 Treatment effectiveness and extrapolation

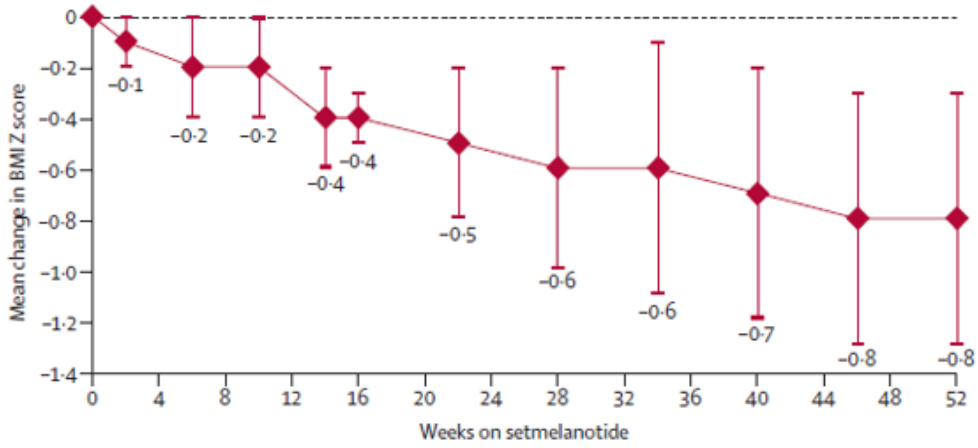
4.2.6.1 Response to treatment

The proportion of paediatric patients who respond to treatment at 14 weeks in the model was estimated to be 85.7% (CS Table 31), based on the proportion of paediatric patients achieving a BMI Z score reduction of ≥0.2 after 52 weeks of setmelanotide from Study RM-493-023 (pivotal patient FAS). For adults a 46.7% response rate is assumed based on the proportion of adult patients with ≥10% weight loss (CS Table 23) from Study RM-493-023 (pivotal patient FAS).

The model assumes responders are assessed at 14 weeks after which point treatment is discontinued for non-responders. It is unclear to the EAG why the company used 52 week data to inform this, rather than data on response at 14 weeks. 14-week response data is not presented in the CS, however BMI-Z scores continue to fall after 14 weeks (Figure 4, CS Fig 10), which would suggest that the proportion of responders may be lower at 14 weeks. We explore the effect of a lower response rate of 80% for paediatrics in a scenario analysis.

Initially the model wasn't properly implementing the response rate (so 100% of patients were effectively responding), however this was fixed in the companies updated model following clarification questions.

Figure 4 Mean change in BMI Z-score from active treatment baseline in BBS patients <18 years (Study RM-493-023, pivotal patient FAS) (CS Fig 10)



4.2.6.2 BMI-Z / BMI categories

The distribution of initial BMI-Z / BMI categories are taken from the baseline characteristics of BBS patients in Study RM 493-023 (pivotal patient SAS, CS Table 13). All patients who respond to treatment are assumed to achieve a reduction in BMI-Z / BMI class of [redacted] for paediatrics and [redacted] for adults. Patients maintain this BMI-Z / BMI reduction for the remainder of the model unless they discontinue treatment, in which case they return to their initial BMI-Z / BMI category, modelled by categorising all patients not on setmelanotide according to the initial BMI-Z BMI distribution.

The EAG was concerned that a [redacted] drop in BMI-Z class may be over estimating the treatment effects in comparison to the continuous outcome measures. Forsythe et al 2021[15] reports a mean change in BMI-z for paediatric patients (n=9) of -0.7 which seems to correspond to a [redacted] change in BMI-z classes, rather than the [redacted] change modelled. From the CS Tables 34 and 35, [redacted].

In response to clarification question B12, the company provided some further detail, explaining that [redacted] classified as "not changing level" have an extremely high starting BMI-z (4+), and did show a clinically significant (>0.2 points) reduction in BMI-z. Also, [redacted] showing a decrease [redacted] actually lost [redacted] in BMI-z, but below BMI-z of 2, changes in class requires a 1-point reduction in BMI-z.

The EAG consider the reduction in BMI-Z classes to be uncertain, based on small numbers of patients with variable responses. In addition to this, the estimate of treatment effect is taken from a single arm of Study RM 493-023 without reference to a control group. The control group in Study RM 493-023 only has data until 14 weeks, after which they switch to setmelanotide, however a comparison of the groups is still informative. Figure 5 shows the [redacted] for both groups over time. There is a [redacted] in BMI-Z for both groups initially, but this [redacted] for placebo until patients are switched to setmelanotide when BMI-Z [redacted]. Because of the initial [redacted] in BMI-Z for [redacted] (which can be thought of as a regression to the mean effect) the change in BMI-Z for the placebo group when they switch to setmelanotide is [redacted] than for those originally on setmelanotide, and may be more representative of the real relative treatment effect. The EAG therefore prefer to assume a [redacted] reduction in BMI-Z class for the paediatric BBS population.

Note that an alternative approach would be to use mean change in BMI-Z from the trial and apply this to an assumed continuous distribution of BMI-Z at baseline (eg Normal or log-Normal). The resulting distribution can then be used to estimate the proportion of patients in each BMI-Z class at follow-up.

Key Issue 7: Size of treatment effect on BMI-Z in responders to setmelanotide in the paediatric population

Figure 5 Mean Percentage Change in BMI-z Score (RM-493-023, Pivotal Paediatric Patients With BBS) (CS Clarification Response)

The model assumes that patients continue to stay in the same reduced BMI-Z / BMI class for the remainder of their life whilst taking setmelanotide. This assumes there is no "waning" of the treatment effect where patients BMI-Z / BMI increases again in the longer-term. Whilst there is no long-term evidence available for setmelanotide, our clinical advisors expected there to be some waning of effect on BMI-Z / BMI based on longer-term evidence for GLP-1 receptor agonists which also act on hunger. [23]

In response to clarification question B11, the company argue that they would expect patients to discontinue treatment if there was a waning of treatment effect, however there may be a gradual waning of effect which would not lead to immediate discontinuation of treatment. The company model some attenuation of effect through a discontinuation rate, where patients who discontinue return to their original BMI and hyperphagia state. However, this does not capture patients who may experience some reduced benefit of treatment on BMI-Z / BMI but remain on treatment and incur the treatment costs. There is functionality in the model to include waning, where a proportion of patients return to their initial BMI-Z / class, but still incur treatment costs and the benefits of mild hyperphagia (ie the waning if for BMI-Z / BMI and not hyperphagia). The EAG consider some form of waning of effect to be appropriate and explore this in a scenario analysis. However, the EAG do acknowledge that the evidence for GLP-1 receptor agonists show only a small waning of treatment effect at 104 weeks compared with 52,[23] suggesting that interventions that act on hunger have the potential to achieve sustained effects in the short to medium term.

Key Issue 8: BMI-Z / BMI reduction is extrapolated into the long-term

4.2.6.3 Hyperphagia state

The baseline hyperphagia distribution was assumed to be 100% severe hyperphagia. All patients that respond to treatment at 14 weeks move to the mild hyperphagia state, and remain there for the remainder of their lifetime while on treatment. Non-responders remain in the severe hyperphagia state.

As discussed in section 4.2.3 and section 2.2 (Key Issue 1), the EAG heard that setmelanotide may be used in those with moderate hyperphagia, and so run a scenario where 60% have severe and 40% have moderate hyperphagia initially, based on the company's response to clarification question B2.

The assumption that all patients who respond to treatment move from the severe to the mild hyperphagia state is likely to be an over-simplification, and some patients may be expected to move to a moderate hyperphagia state (Key Issue 6). This is supported by the variability across patients in % change in most/worst hunger in adults in Study RM 493-023 (CS Table 42). We would expect that changes in hyperphagia would be linked to changes in BMI-Z / BMI class, with patients who have a bigger response on hyperphagia also having a bigger response on BMI-Z / BMI class. We therefore ran a scenario where responders move

to either mild or moderate hyperphagia, with [redacted] moving to mild (the proportion moving 2 BMI-Z classes in CS Table 35), and [redacted] to moderate.

4.2.6.4 Treatment discontinuation

The company assume that patients who do not respond discontinue treatment at 14 weeks. Patients who respond at 14 weeks are assumed to remain on treatment long-term, but with a 1% annual discontinuation rate. Patients who discontinue are then modelled as for the BSC arm with BMI-Z / BMI and hyperphagia returning to the initial values. The 1% discontinuation rate is an assumption based on the value previously used in NICE HST21 for setmelanotide in patients with obesity caused by LEPR / POMC deficiency.[19] A discontinuation rate of 1% was an assumption made by the EAG (PenTAG) for HST21, considered reasonable by their clinical advisors, and chosen to represent discontinuation "due to the burden of constant injections and/or adverse events (in particular skin pigmentation which may result from setmelanotide use)." In response to our clarification question B13, the company explain other possible reasons for discontinuing setmelanotide including patients whose hyperphagia was no longer controlled and as a consequence they were regaining weight.

The EAG agrees that an annual discontinuation rate should be included in the model, although prefers to use data from the companys studies on BBS patients to inform this. In response to clarification B16 the company provided further detail on discontinuation in Study RM-493-023. [redacted] discontinued whilst taking setmelanotide by week 52, of which [redacted] were due to adverse events and [redacted] due to lack of efficacy. Based on the FAS dataset of 43 patients, this gives a treatment discontinuation rate of [redacted]/43=[redacted] due to adverse events and [redacted]/43=[redacted] due to lack of efficacy. The EAG acknowledges that discontinuation due to adverse events may occur soon after treatment is initiated, and/or managed using dose titration. However, we consider that there is uncertainty in the treatment discontinuation rate over time, and this may be higher than 1%. This is particularly important as the company use discontinuation rate as a proxy for waning of treatment efficacy over time in their model (see section 4.2.6.2). We ran a scenario analysis using a discontinuation rate of 2%.

4.2.6.5 Obesity-related co-morbidities

Obesity-related comorbidities for the BBS population were modelled according to the literature on general obese patients with sleep apnoea,[25, 26] osteoarthritis,[27] cardiovascular events (myocardial infarction (MI), Angina, Stroke, transient ischaemic attack (TIA))[28-30] and non-alcoholic fatty liver disease (NAFLD).[31, 32] The distribution of the proportions of patients with co-morbidities was assumed to be dependent on BMI-Z / BMI class, in part based on published literature,[25, 27, 31, 32] and in part using linear extrapolation where information was not available (section B.3.3.3 of CS). The prevalence of co-morbidities in paediatrics was based on the prevalence for adults by directly mapping the lower and upper BMI categories to the lower and upper BMI-Z categories, and then using linear extrapolation to obtain prevalence for BMI-Z categories in between those bounds.

The EAG recognises that there is a lack of data to model the impact of BMI-Z / BMI on co-morbidities specifically in BBS patients, and considers the use of data from a general obese population to be a pragmatic approach, which is also in line with the approach taken and accepted in NICE HST21.[19] A mix of different evidence sources together with linear extrapolation was used for the prevalence of co-morbidities, which may lack generalisability to a UK BBS population, and relationships may be non-linear leading to biased extrapolations. The EAG is also concerned about the strong assumptions made by applying prevalence in adults to estimate prevalence in children, which is unlikely to be appropriate. In particular obesity-related osteoarthritis is unlikely to occur in children and younger adults.

We note that concerns with generalisability of the evidence sources were raised by the EAG for HST21,[19] but scenario analyses showed that the results were not sensitive to changes in assumptions around prevalence of co-morbidities. We therefore consider that although there is uncertainty around the prevalence of obesity-related co-morbidities in a BBS population, the alternatives to the approach taken by the company are unlikely to have a large effect on the ICER.

4.2.6.6 Mortality

Due to lack of data specific to a BBS population, mortality was modelled using UK general population life tables, using Standardised Mortality Rates (SMR) from a large UK cohort[33] to adjust for BMI class in adults, and a prospective cohort study of 41,359 Swedish children to adjust for BMI-Z class in children[34] (Table 60 CS). Log-linear models were used to obtain SMRs by BMI-Z class, calibrated to the overall SMR from Lindberg 2020.[34] The company also applied a further SMR of 85% to patients who are receiving setmelanotide to reflect benefits on non-obesity-related BBS symptoms, which the company clarified might include choking, gastric rupture and/or respiratory illness[35].

In the model therefore, setmelanotide reduces mortality in two ways. Firstly resulting from being in a lower BMI-Z / BMI class, and secondly through a reduction in non-obesity related BBS symptoms. The EAG considered the survival benefit via BMI-Z / BMI class to be appropriate to capture the potential benefits of setmelanotide. However, we heard from our clinical advisors that it would be unlikely that setmelanotide would have an additional survival benefit other than through its effect on obesity, and so consider this to be doubtful. In response to clarification questions the company have sent the SMR for a reduction in non-obesity-related BBS symptoms on setmelanotide to be 1 in their updated model, which has a limited impact on the base case changes the ICER from £191,759 to £191,596. Note also that this SMR parameter is not properly linked in the probabilistic part of the model, however since the company have changed this SMR to 1 then this doesn't impact the results reported below.

4.2.7 Health related quality of life

The company undertook an independent systematic review to identify relevant studies reporting HRQoL. The review identified three studies (seven reports) as eligible for inclusion in their review, but the company report that 'No HRQoL data suitable for inclusion in the economic model were identified'(CS, B.3.4.3, p123).

The systematic review, as conceptualised and reported in the CS, does not fully align with the comparison made in the model. The review focuses on paediatrics and adults with obesity or hyperphagia caused by BBS and the model requires outcome data from obese compared with non-obese children without BBS. These are different populations which would require a different literature search and systematic review. Since the review presented by the company does not inform the development of the model, we do not report a full critique of the review beyond noting this issue.

4.2.7.1 Utilities by age and BMI / BMI-Z category

The CS argues that HRQoL data collected directly from the EQ-5D questionnaires completed by BBS patients in Studies RM-493-023 and RM-493-022 is not appropriate to use in the model because the EQ-5D is insensitive to important changes in HRQoL brought on by the decrease in hyperphagia. The CS further argues that because patients are born with BBS, and may experience hyperphagia all their lives, they may adapt to their condition and not fully realise the impact on their HRQoL. The CS therefore solely relies on utility data obtained from external studies to inform the model.

The impact on HRQoL due to obesity was obtained from the Riazi 2010[20] study. This is a UK observational comparative cross-sectional study of obese (n=96) and non-obese (n=444) children and adolescents who completed age appropriate PedsQL v4.0 questionnaires. The CS mapped PedsQL subscale scores reported for children aged 8-18 in this study to EQ-5D-3L utility scores using Khan's 2014[22] linear regression model 5 mapping algorithm. Obese and non-obese mapped scores were used to inform utilities for the highest and lowest BMI categories in the CS model; and the intermediate categories were linearly extrapolated (Table 63 in CS).

The CS model accounts for ageing by using adult utilities when patients turn 18, informed by Alsumali (2018) study on bariatric surgery for morbid obesity.[21] Alsumali 2018[21] reported BMI-specific, age stratified utilities (in Table 63 of CS) calculated in Sullivan and Ghushchyan 2006[36] by approximating EQ-5D values to the SF-12 values reported on the from the Medical Expenditure Panel Survey in the USA.[37]

The EAG agrees that the EQ-5D questionnaire may not be sensitive to pick up the improvement in quality of life from reduced hyperphagia. The EAG also agrees that patients born with BBS would have adapted to living with hyperphagia and not may realise the full decrement in HRQoL it may take. The CS does not make the case for why other HRQoL measures collected in the RM-493-023 trial, such as the PedsQL for children and the SF 12/36 and the IWQoL for adults, would also fail to pick up meaningful improvements in

HRQoL from hyperphagia. By using mapped PedsQL scores from an external population, the CS is assuming that the distribution of scores in the different subscales comprising the PedsQL total score would be the same in the external and BBS population, which may not be the case.

The EAG acknowledges that at the time of HST21 appraisal, there was no superior source for HRQoL data in the BBS population which could have picked up the health benefits of reduced hyperphagia. Therefore, applying utilities mapped from a different population, albeit with potentially different subscale combinations, would have been the best available source of data at the time. However, since then, Forsythe et al (2023)[1] reported the PedsQL v4.0 scores in BBS children and adolescents (n=9) and the IWQOL in adults (n=11) from the RM-493-023 trial who successfully reduced weight while using setmelanotide for 12 months. SF12/36 data were not reported. These data would have been a superior source of data in the hierarchy of preferred HRQoL methods described in the NICE reference case.[11] Although in a small sample of 20 patients, the authors conclude that 12 months of setmelanotide produces clinically meaningful improvements across multiple HRQoL measures in the BBS population and that these were correlated with changes in BMI. The EAG requested the PedsQL data in the RM-493-023 trial patients (n=9) to be mapped onto EQ-5D utilities using the same Khan (2014) [22] algorithm that the CS applied to map PedsQL estimates from Riazi et al (2010).[20] In the clarification response, the company argued that the dataset was too small to allow for this mapping. It is unclear why it is not possible for the company to apply an algebraic algorithm to the patients' PedsQL subscale scores in the RM-493-023 trial as they did to the mean scores reported in Riazi (2010).[20] Forsythe et al (2023)[1] does not report the results of all subscales of the PedsQL questionnaire to allow the EAG to map those scores on to EQ-5D utilities using Khan's algorithm.

Khan's 2014 mapping algorithm[22] has been widely used to map PedsQL scores to EQ-5D utilities in children and adolescents across numerous clinical areas. Models 5 and 6 are the best fitting models, where 6 allows for adjustments for age and sex. Those data are not available from the Riazi 2010 study but would have been available for the RM-493-023 trial patients. The algorithm was derived from a sample of 559, mostly healthy children aged 11-15 in England, and can be applied to PedsQL responses in children as young as 2 years old.

The EAG attempted to use mapped PedsQL scores on to EQ-5D utility scores from another paediatric population in the literature to approximate to the utility values that would have been mapped from the total PedsQL scores reported in the Forsythe[1] study. This is described in Appendix 3 (section 0). It would also be possible to map SF12 or SF36 trial data to EQ-5D utilities, or triangulate it with IWQoL data to inform the adult utilities in the model. The lack of HRQoL data reported for adult BBS patients meant that a change in the model structure to avoid the hyperphagia multiplier was not possible to implement, and the EAG has therefore not pursued this method to approximate utilities in our scenarios.

The EAG note that there is functionality in the CS Excel model to select an "Trial EQ-5D-5L" for the BMI utility measure inputs to the model. However, it is unclear to the EAG where these values come from and which valuation was used for the 5L responses, as they are not mentioned in the CS or referenced in the model. Furthermore, a hyperphagia multiplier and a BBS multiplier are still applied when this option is selected, which will mean that there is double counting of these utilities. Selecting the "Trial EQ-5D-5L" option reduces the company base-case ICER, however the EAG is uncertain what the values are based on and consider the approach to inappropriately double count utilities for hyperphagia and BBS non-obesity-related comorbidities.

In summary, HRQoL data collected in RM-493-023 remains the only source of HRQoL data available for patients with BBS before and after being prescribed setmelanotide. Changes in these scores should reflect the health benefits experienced by BBS patients from living with reduced hyperphagia. The EAG considers that utilities derived from the trial HRQoL data are preferable and should have been presented in a scenario analysis. They would have avoided the need to rely entirely on utility data from an external population without the condition, where hyperphagia multipliers were applied based on a vignette study.

Key Issue 9: Evidence sources for health-state utilities

4.2.7.2 Utility decrements due to hyperphagia

The utility for hyperphagia is modelled as a multiplier of the baseline utility for the different age and BMI categories. The utility weights for hyperphagia were estimated from a Vignette Study[38] of 215 healthy adults from the general UK population using a time-trade off approach for 4 hyperphagia health states. The company use a conservative approach which sets all negative utilities to zero when estimating the utility for the severe hyperphagia state. This gives a utility multiplier of 0.98 for no hyperphagia, 0.91 for mild hyperphagia, 0.72 for moderate hyperphagia and [redacted] for severe hyperphagia. The CS cites the precedent of using this vignette study in NICE HST21 for setmelanotide in patients with obesity caused by LEPR or POMC deficiency.[19]

The EAG acknowledges that the vignette study was accepted as a source of utilities in NICE HST21.[19] The vignette study to capture hyperphagia was performed according to DSU methodology, but superior sources of utility data are now available for this study (section 4.2.7.1). The EAG would prefer the company to use mapped PedsQL scores for the BBS children in RM-049-023 (Key Issue 9).

4.2.7.3 Utility ceiling effect due to BBS

A BBS specific utility multiplier of 0.8 was applied which effectively creates a ceiling effect for utilities for BBS patients, to capture the impact of non-obesity-related co-morbidities such as retinal disease or blindness, renal failure, and cognitive impairment. The value of 0.8 was an assumption made by the company.

The EAG agree with the company that BBS patients carry a considerable burden of non-obesity-related co-morbidity, and it is appropriate to include a utility multiplier. The EAG wonder whether it would be possible to use the HRQoL collected in RM-493-023 together with a matched cohort of non-BBS patients to obtain a crude estimate of the BBS specific utility multiplier. An alternative would be to use a similar approach used by the company for obesity-related comorbidities, based on prevalence of non-obesity-related comorbidities in BBS patients and literature-based disutilities. In the absence of further information on this, the EAG run scenario analyses to different values of the utility multiplier (0.7 and 0.9).

Key Issue 10: Utility multiplier for BBS patients due to non-obesity-related comorbidities.

4.2.7.4 Utility decrements due to obesity-related comorbidity

Comorbidity related utilities are applied as additive utility decrements[39] for sleep apnoea, osteoarthritis, cardiovascular events (MI, Angina, Stroke, TIA) and NASH. The same sources were used as in the NICE TA for liraglutide in the management of overweight and obesity and HST21 for setmelanotide for treatment of obesity caused by LEPR/POMC deficiency.[19]

The EAG recognises that these sources for utilities have been previously accepted in NICE appraisals, and seem appropriate for use here.

4.2.7.5 Utility decrements due to side effects of setmelanotide

The company did not include any TEAEs in their original model, despite [redacted] of patients receiving setmelanotide reporting a TEAE by 52 weeks. In response to clarification question B19 the company explained that the TEAEs were skin hyperpigmentation ([redacted]), injection site erythema ([redacted]), nausea ([redacted]) and vomiting ([redacted]), and that nausea and vomiting were mild and transitory, resolving during the titration period. The company updated their model to include disutilities for nausea, vomiting and injection site reaction, but argues that skin hyperpigmentation is not necessarily unwelcome. The disutilities are applied for 14 weeks in the model (although it says 2 weeks in company response to B19) to [redacted] for nausea and vomiting[40] and to [redacted] for injection site erythema, [41] as per reported side-effect RM-493-023 trial, with negligible impact to the ICER (changing from £191,759 to £191,797).

The EAG prefers the inclusion of TEAEs in the model, although note this only has a small effect on the ICER. The EAG accepts that nausea and vomiting may be transitory, however, injection site reactions might be expected to continue while patients are receiving setmelanotide. The impact of including a long-term disutility for injection site reactions is unlikely to have a large impact on the ICER. Although it is possible that skin hyperpigmentation could have a disutility for the duration of the patients' treatment on setmelanotide, the impact on the ICER would be negligible.

EAG considers the disutilities applied in the updated version of the model to be reasonable.

4.2.7.6 Utility decrements in carers

The model include a disutility decrement of 0.0986 per carer, which followed estimates used in previous NICE submissions.[42, 43] The CS has assumed an average of 1.5 caregivers per paediatric patient and 1 per adult patient.

The EAG agrees that carer burden should be included in the model due to the high impact on HRQoL of BBS to families. Carer disutility burden is high, causing the model to accrue negative QALY gains in the first 11 years. Clinical advice to the EAG suggested that applying a disutilities for an average of 1.5 carers in childhood would be reasonable. The EAG clinical advisors noted that carers have less control of BBS patients' diet and lifestyle as adults, and the carer burden in the adult BBS population is mostly due to non-obesity related conditions such as eye problems and cognitive impairment. The EAG heard that the number of carers for adult BBS patients is variable and ranges from zero to two for the very few patients with severe disability, with an average of 0.5 considered reasonable. The EAG explored assumptions to lower average number of carers for adults to 0.5 and 0.8 in scenario analyses.

Key Issue 11: Average number of carers for adult BBS patients

4.2.8 Resources and costs

The model includes treatment costs, annual monitoring costs, and costs related to treating comorbidity and cardiac events in the paediatric and adult populations. Unit costs for resource use were updated to the most recent estimates in the updated version of the model after clarification questions.

4.2.8.1 Setmelanotide costs

The unit cost for setmelanotide is [redacted], a [redacted] discount on the reference NHS list price. Daily costs per dose are estimated separately for the first and subsequent years whilst on the drug (Table 14), with the average dose being different for paediatrics and adults. Year 1 costs are based on an average of starting dose, predicted titration dose, and post-titration dose. Year 2 and subsequent costs are based on the predicted titration dose. It is assumed that administration costs are negligible, and there would be no wastage.

Table 14 - Daily treatment costs and dosing

Population	Year 1 daily Cost (£/day) dose (mg/day)	Year 2+ daily cost (£/day) dose (mg/day)
Paediatric	£[redacted] / day [redacted] mg/day	£[redacted] / day [redacted] mg/day
Adult	£[redacted] / day [redacted] mg/day	£[redacted] / day [redacted] mg/day

The EAG considers the approach to estimating treatment cost based on average doses in a titration and subsequent period separately for paediatrics and adults to be appropriate. Patients self-administer the injections with help from care-givers, so would not incur administration costs. Setmelanotide would be used in addition to existing best supportive care (BSC) and no reduction in BSC costs are assumed for patients whilst on setmelanotide, which the EAG considers is likely a conservative assumption as some reduction in BSC costs may occur in those patients with significant reductions in BMI-Z / BMI.

Following clarification questions the company added in disutilities due to treatment-emergent adverse events, however did not include costs of managing these adverse events. The EAG would prefer these costs to be included but does not anticipate that they would have a big effect on the ICER.

4.2.8.2 Monitoring costs

In the companys submission and original model, monitoring costs were assumed to be the same for setmelanotide and BSC with the exception of annual primary care physician monitoring visits which were assumed to be 4 for BSC compared with 1 for setmelanotide (Table 67, CS). After clarification questions, the company updated the physician monitoring visits an additional in the first year and 1 for subsequent years for setmelanotide, with 4 visits per year unchanged for the BSC group. The updated monitoring costs are given in Table 15.

Table 15 – Annual monitoring costs by treatment and year in companys updated model following clarification questions

Treatment Group	Year 1	Year 2+
setmelanotide	£709.00	£457.00
Best Supportive Care	£583.00	£583.00

We agree that the initial prescribing of setmelanotide would occur at a routine annual visit in a BBS clinic, and therefore not different from BSC. Clinical advice received by the EAG suggested that patients would require active monitoring in the first year of treatment, and so the assumptions in the company's updated model are a better reflection of how patients are likely to be managed in the first year, compared with their original model. However, our clinical experts advised that monitoring of patients on setmelanotide would likely occur in secondary care services, local to the BBS patient, and that this would be supported by one of the specialist BBS centres, contrary to the company's assumption of monitoring based in primary care. Because setmelanotide is an add-on therapy to BSC, patients on setmelanotide are unlikely to have less visits per year than BSC in subsequent years, and in fact will likely have an additional annual visit to review progress and prescribing. The EAG recognises that patients on setmelanotide will save primary and secondary care resources by reducing their obesity-related comorbidity, but those cost savings are already accounted

for in the model by reducing the costs and disutilities resulting from cardiac events and comorbidities for patients on setmelanotide.

We therefore run a scenario where after initial prescribing, patients would be monitored in secondary or tertiary care through a weight management clinic at a local hospital. This would result in three additional visits to weight-management clinic during the first year. Monitoring from years 2 onwards would require one additional annual visit to the weight management clinic to review progress and prescribing. The EAG assumes that all other monitoring costs would be the same as for patients in BSC and so the additional monitoring costs occur only in the setmelanotide group. The EAG approximated the cost of a weight management clinic to the unit cost for the health care resource group code for a Dietetics consultant led outpatient clinic (£96, service code 654 in the National Collection of Costs published in 2022).[44] The EAGs adjusted annual monitoring costs by adding the incremental costs of visits in secondary care (£96-£42 for the physician visit in primary care included in the CS) to obtain the monitoring costs in Table 16.[45]

Table 16 – EAG preferred assumptions for annual monitoring costs by treatment and year in companys updated model

Treatment Group	Year 1	Year 2+
setmelanotide	£871.00	£679.00
Best Supportive Care	£583.00	£583.00

4.2.8.3 Health-state and comorbidity costs

Health state costs by BMI-Z / BMI class come from an economic evaluation based upon UK Biobank data that included both primary and secondary healthcare.[46] These were assumed constant across age in the paediatric population (Table 69, CS), and are estimated by age group in the adult population (Table 70, CS) using the reported age interaction Mendelian randomisation and multivariable adjusted analysis. [46]

The EAG considered the approach to estimating costs by BMI-Z / BMI appropriate.

The CS undertook a targeted literature search to identify comorbidity-related costs in a general obese population. Costs were included for cardiac events, sleep apnoea, osteoarthritis, NASH, and T2DM (Tables 71 and 72 of CS) taken from a variety of sources. Costs for the paediatric population were informed mostly from literature on adult patients.

The EAG notes that the costs for sleep apnoea are estimated from a study of older people,[47] and so may not generalise to younger and paediatric patients. The costs for T2DM are estimated from a population type 2 diabetes adult patients with an average BMI of 29, which is likely to be lower than for BBS patients.[48] The generalisability of these data sources to obese BBS patients is therefore uncertain, especially for paediatrics. However, the EAG agrees that in the absence of BBS-specific evidence, then using data from general adult

obese populations is the best option available. The EAG also notes that most of the co-morbidity costs were identical to those assumed in HST21 for setmelanotide for treatment of obesity caused by LEPR/POMC deficiency,[19] so there is a precedent for using these costs.

4.2.9 Uncertainty analysis

The company conducts a probabilistic sensitivity analysis (PSA) to explore the impact of uncertainty on the results. Standard errors were calculated using source data, where available, and a 10% standard error was assumed for variables where cohort size was unavailable.

The EAG is happy with the distributions chosen for the PSA, however, note that a 10% standard error may not properly reflect the full range of plausible values, and so not fully capture uncertainty. The range of values presented in the one-way sensitivity analysis is also limited by the choice of 10% standard error, and the resulting ICER range may not reflect the full range of values that may be plausible.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

In response to clarification questions the company made the following changes to their base-case model:

- The QALY calculation was corrected so that non-responders on setmelanotide receive no hyperphagia treatment effect in first cycle of the model
- The equations in the cost and clinical outcomes sheet were corrected to consistently switch to BMI from BMI-z at age 18.
- The SMR for non-obesity related mortality on setmelanotide was set to 1.
- Unit costs were updated to reflect the most recent available data.
- Monitoring costs on setmelanotide were updated to an [redacted] additional physician visits in year 1 compared with BSC
- Disutilities were incorporated for nausea/vomiting and injection site erythema for setmelanotide patients during the first 2 weeks of treatment.

All results in this report are based on the company's updated model which the EAG received on 8th March 2023. The majority of company's results are deterministic (in line with what they present in their report), but all the EAG scenarios and base-case results are from a probabilistic analysis.

The companys base-case results for the incremental cost-effectiveness analysis for setmelanotide in paediatric patients with BBS are presented in Table 17.

Table 17 Base-case cost-effectiveness analysis deterministic results for setmelanotide in paediatric patients with BBS (companys updated model)

	setmelanotide	Best supportive care
Total cost	[redacted]	£117,310
Total life-years gained	[redacted]	24.12
Total quality-adjusted life years	[redacted]	0.93
Total undiscounted quality-adjusted life years	[redacted]	2.90
Incremental costs	[redacted]	
Incremental life years gained	[redacted]	
Incremental quality-adjusted life years	[redacted]	
Incremental undiscounted quality-adjusted life years	[redacted]	
Incremental cost-effectiveness ratio	£194,495/QALY	

5.2 Company's sensitivity analyses

The results from the probabilistic sensitivity analysis (PSA) based on 1000 iterations are presented in Table 18, and the cost-effectiveness plane in Figure 6, for the company's updated base-case. The cost-effectiveness acceptability curve in Figure 7 shows that at a threshold of £195,000, setmelanotide becomes more likely to be cost-effective than BSC.

Table 18 Base-case cost-effectiveness analysis probabilistic results for setmelanotide in paediatric patients with BBS (companys updated model)

	setmelanotide	Best supportive care
Total cost	[redacted]	£117,055
Total life-years gained	[redacted]	24.13
Total quality-adjusted life years	[redacted]	1.00
Incremental costs	[redacted]	
Incremental life years gained	[redacted]	
Incremental quality-adjusted life years	[redacted]	
Incremental cost-effectiveness ratio	£194,072/QALY	

Figure 6 Probabilistic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide in paediatric patients with BBS (companys updated model)

Figure 7 setmelanotide cost-effectiveness acceptability curve for use in paediatric patients (companys updated model)

The company conducted one-way deterministic sensitivity analysis on inputs, variation detailed in table 77 of the CS report. The impact on incremental cost-effectiveness ratio from each one-way variation in a parameter/ groups of parameters is displayed in the

tornado diagram Figure 8. The parameters with greatest impact are baseline severity of hyperphagia, baseline age, treatment cost/mg, baseline distribution of obesity , hyperphagia utility multiplier, BBS QALY multiplier and the treatment effects on severity of hyperphagia.

Figure 8 One-way deterministic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide vs BSC in paediatric patients (company's updated model)

5.3 Company's scenario analyses

Seven scenario analyses were included in the CS (described in CS section B.3.10.3), the results of which are presented in Table 19 for the CS updated base case. However, there was no functionality in the model sent to the EAG to run the scenarios for increased BSC costs by increased obesity level and caregiver productivity costs. We were therefore unable to run these, however would expect that the patterns seen for these two scenarios in relation to the base-case in the CS (CS Table 81) would be similar in the company's updated base-case.

Table 19 Cost-effectiveness results scenario analyses (updated CS model), deterministic results

Scenario	ICER (£/QALY)
Companys Base-Case (updated model)	£194,495
Uniform baseline BMI/BMI Z-score category distribution.	£198,781
Increased BSC costs by £25 for increasing obesity level.	-
Comorbidity disutilities decreased by 10% as presented in (Table 79 of CS).	£196,628
Severe obesity utility decreased by 0.05 as presented in (Table 80 of CS).	£194,121
1.5% discount rate for benefits.	£131,387
Reduced hyperphagia treatment effect.	£223,149
Caregiver productivity cost	-

5.4 Subgroup Analysis

A subgroup analyses was conducted for an adult population in which the baseline BMI distribution was: [redacted] of patients were of BMI category 30 to <35 kg/m^2; [redacted] were 35 to <40 kg/m^2; [redacted] were 40 to <45 kg/m^2, [redacted] were 45 to <50 kg/m^2, and [redacted] were ≥50 kg/m^2. In adults 46.7% were assumed to be responders (Table 8), who obtain a reduction of [redacted] BMI category. Cost-effectiveness analysis results for the adult population in the company's updated model are presented in Table 20.

The company also present results for a mixed population 60% paediatric patients and 40% adult patients, displayed in Table 21 for company's updated model.

Table 20 Cost-effectiveness analysis deterministic results adult population (updated CS model)

	setmelanotide	Best supportive care
Total cost	[redacted]	£130,870
Total life-years gained	[redacted]	20.71
Total quality-adjusted life years	[redacted]	0.56
Total undiscounted quality-adjusted life years	[redacted]	0.97
Incremental costs	[redacted]	
Incremental life years gained	[redacted]	
Incremental quality-adjusted life years	[redacted]	
Incremental undiscounted quality-adjusted life years	[redacted]	
Incremental cost-effectiveness ratio	£223,053/QALY	

Table 21 Cost-effectiveness analysis deterministic results mixed population 60% paediatric patients and 40% adult patients (updated CS model)

	setmelanotide	Best supportive care
Total cost	[redacted]	£122,734
Total life-years gained	[redacted]	22.75
Total quality-adjusted life years	[redacted]	0.78
Total undiscounted quality-adjusted life years	[redacted]	2.12
Incremental costs	[redacted]	
Incremental life years gained	[redacted]	
Incremental quality-adjusted life years	[redacted]	
Incremental undiscounted quality-adjusted life years	[redacted]	
Incremental cost-effectiveness ratio	£201,081/QALY	

5.5 Model validation and face validity check

The economic model was validated following the TECH-VER checklist, an accepted validation guideline (Büyükkaramikli 2019).[49] Model validation included checking calculations and features for consistency and face validity, detailed checks on formulae, and assessment of validity of model functionality and macros. Thus, the review included black- and white-box testing. Event/state calculations, result calculations, uncertainty analysis, and overall tests of model functionality, transparency and validity were performed. This picked up some issues that were raised with the company in clarification questions (B6 – B9, Clarification questions document). In response, the company updated their model as described in section 5.1. Repeat internal and external model validations were conducted on the companys updated model to reassess all updated model functionality and equations, and no further issues were identified. We would used Spreadsheet Detective, Southern Cross Software to help check the Excel model.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

All of the EAGs scenario and base-case analyses are applied to the company's updated base-case model received by the EAG on 8th March 2023 in response to clarification questions. All results shown are from a probabilistic analysis.

The EAG conducted the following additional scenarios:

- Scenario 1: Initial severity of hyperphagia
  The company assumes that all patients treated with setmelanotide will suffer from severe hyperphagia, independent of BMI-Z / BMI. As discussed in section 4.2.3 the EAG

considers it more appropriate to assume a proportion of patients have moderate hyperphagia. We explore a scenario where 60% of patients have severe hyperphagia initially, and 40% have moderate hyperphagia, based on the company's response to clarification question B2.

- Scenario 2: Treatment discontinuation
  The company assume 1% of patients discontinue treatment each year, based on an assumption made by the EAG (PenTAG) for HST21.[19] The EAG prefers to use base this on data available from the companys study, which suggests there may be a higher discontinuation rate (as discussed in section 4.2.6.4). The EAG explores this with a scenario using a discontinuation rate of 2%.

- Scenario 3: Treatment effect on hyperphagia
  The company assumes that all patients who respond move to a mild hyperphagia state, regardless of their change in BMI-Z / BMI. As discussed in 4.2.6.3, the EAG considers this an oversimplification, and would expect that some patients may move to a moderate hyperphagia state, and this is likely to be related to the proportion of patients experiencing a smaller reduction in BMI-Z / BMI. We therefore ran a scenario where responders move to either mild or moderate hyperphagia, with [redacted] moving to mild (the proportion moving 2 BMI-Z classes in CS Table 35), and [redacted] to moderate.

- Scenario 4: Treatment effect on BMI-Z
  The company assumes that all paediatric patients who respond to treatment achieve a reduction in BMI-Z / BMI class of [redacted]. As discussed in section 4.2.6.2, the EAG prefer a [redacted] reduction in BMI-Z class for the paediatric BBS population, which we explore in a scenario.

- Scenario 5: Number of carers for adults
  The company assumes 1 carer per adult patient. The EAG consider that not all adults will require a carer, and prefer to assume 0.5 carers per adult patient as discussed in section 4.2.7.6. We run scenario analyses to (a) 0.5 carers and (b) 0.8 carers.

- Scenario 6: BBS utility multiplier
  The company apply a BBS specific utility multiplier of 0.8 which creates a ceiling for utilities for BBS patients. As discussed in section 4.2.7.3 the EAG agree that use of a BBS utility multiplier is appropriate, but the choice of 0.8 is arbitrary. We run scenario analyses to different values of (a) 0.9 and (b) 0.7.

- Scenario 7: Monitoring costs for setmelanotide
  The company assumes [redacted] additional visits in the 1st year and [redacted] less in subsequent years for setmelanotide compared with BSC, and costs these as primary care visits. As discussed in section 4.2.8.2, EAG clinical experts advised monitoring costs would occur exclusively in secondary or tertiary care, and that there would be an additional visit in

years 2+ to review progress and the prescription. We adjust this in a scenario using the physician monitoring visit costs in Appendix 1.

- Scenario 8: Waning of treatment effect
  The company assumes that patients BMI-Z / BMI reduction is maintained whilst taking setmelanotide. The EAG considers it unlikely that there wouldn't be some waning of effect, as discussed in section 4.2.6.2. There is functionality in the model to include waning, whereby a proportion of patients return to their initial BMI-Z / class, but still incur treatment costs and the benefits of reduced hyperphagia. In the absence of any evidence on which to base assumptions about treatment effect waning, the EAG have used a 1% waning effect in a scenario analysis to explore the impact of waning.

- Scenario 9: Setmelanotide response rate
  The company assumes a 14week response rate based on 52 week data. As discussed in 4.2.6.1, the response rate may be lower at 14 weeks than at 52 weeks. To explore this we run a scenario analysis with a response rate of 80%.

6.1.1 Additional exploratory analyses that were not possible to implement by the EAG

In Appendix 3 (section 0), the EAG sets out an attempt to approximate a mapping exercise for the PedsQL scores from Forsythe 2023[1] onto EQ-5D utilities. Using these utility estimates it would no longer be necessary to make adjustments for hyperphagia and BBS multipliers. Unfortunately, there is currently no algorithm to map IWQoL scores for the adult population to the EQ-5D utilities. Mapping these IWQoL scores would require further triangulation of data which were not available to the EAG.[50, 51] The EAG were therefore unable to explore the impact of using the PedsQL data from Forsythe 2023.[1]

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results from the EAGs scenario analyses are shown for the paediatric population in Table 22 and for the mixed (60% paediatric, 40% adult) population in Table 23. Not all scenarios can be combine together, we therefore show the effect of combining scenarios 2, 3, 4, 5a, 6a, 7, 8, and 9.

Table 22 EAGs additional scenario analyses applied to the Company's updated base case model paediatric population (probabilistic results displayed)

No.	Scenario	Incremental Costs	Incremental QALYs	Incremental undiscounted QALYs*	ICER
0	Company's base case (probabilistic)	[redacted]	[redacted]	[redacted]	£194,072

1*	Initial severity of hyperphagia	[redacted]	[redacted]	[redacted]	£230,084
2	Treatment discontinuation	[redacted]	[redacted]	[redacted]	£194,200
3	Treatment effect on hyperphagia	[redacted]	[redacted]	[redacted]	£217,863
4	Treatment effect on BMI-Z	[redacted]	[redacted]	[redacted]	£207,320
5a	Number of carers for adults 0.5	[redacted]	[redacted]	[redacted]	£205,202
5b	Number of carers for adults 0.8	[redacted]	[redacted]	[redacted]	£197,532
6a	BBS utility multiplier 0.9	[redacted]	[redacted]	[redacted]	£179,429
6b	BBS utility multiplier 0.7	[redacted]	[redacted]	[redacted]	£213,869
7	Monitoring costs for setmelanotide	[redacted]	[redacted]	[redacted]	£196,088
8	Waning of treatment effect	[redacted]	[redacted]	[redacted]	£200,092
9	setmelanotide response rate	[redacted]	[redacted]	[redacted]	£196,077
All	2 + 3 + 4 + 5a + 6a + 7 + 8 + 9	[redacted]	[redacted]	[redacted]	£231,683

**Note incremental undiscounted QALYs calculated at a later date with a new simulation to the other results in the table, and so may differ within simulation error*

Table 23 EAGs additional scenario analyses applied to the Company's updated base case model mixed 60% paediatric and 40% adult population (probabilistic results displayed)

No.	Scenario	Incremental Costs	Incremental QALYs	Incremental undiscounted QALYs	ICER
0	Company's base case (probabilistic)	[redacted]	[redacted]	[redacted]	£200,845

1*	Initial severity of hyperphagia	[redacted]	[redacted]	[redacted]	£236,800
2	Treatment discontinuation	[redacted]	[redacted]	[redacted]	£200,864
3	Treatment effect on hyperphagia	[redacted]	[redacted]	[redacted]	£226,398
4	Treatment effect on BMI-Z	[redacted]	[redacted]	[redacted]	£211,636
5a	Number of carers for adults 0.5	[redacted]	[redacted]	[redacted]	£214,717
5b	Number of carers for adults 0.8	[redacted]	[redacted]	[redacted]	£205,827
6a	BBS utility multiplier 0.9	[redacted]	[redacted]	[redacted]	£184,545
6b	BBS utility multiplier 0.7	[redacted]	[redacted]	[redacted]	£220,355
7	Monitoring costs for setmelanotide	[redacted]	[redacted]	[redacted]	£202,701
8	Waning of treatment effect	[redacted]	[redacted]	[redacted]	£205,623
9	setmelanotide response rate	[redacted]	[redacted]	[redacted]	£202,102
All	2 + 3 + 4 + 5a + 6a + 7 + 8 + 9	[redacted]	[redacted]	[redacted]	£241,291

6.3 EAG's preferred assumptions

The EAG's preferred assumptions are:

1. 2% discontinuation rate (Scenario 2)
2. Treatment effect on hyperphagia with [redacted] moving to mild and [redacted] to moderate (Scenario 3)

3. Treatment effect on BMI-Z of a [redacted]-level reduction in BMI-Z class for the paediatric BBS population (Scenario 4)
4. 0.5 care-givers for adult patients (Scenario 5a)
5. Secondary/tertiary care costs for monitoring visits in weight-management clinics setmelanotide group in the first and subsequent years (Scenario 7)

The results for the for the EAGs preferred assumptions are shown for the paediatric population in Table 24 and for the mixed (60% paediatric, 40% adult) population in Table 25 , where each assumption is added incrementally to culminate with the EAG base-case.

Table 24 Cost-effectiveness results for the EAGs preferred assumptions added incrementally and base case paediatric population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs*	Total QALYs	Incremental Costs	Incremental undiscounted QALYs*	Incremental QALYs	ICER
Companys base-case (probabilistic, updated model)							
BSC	£117,055	2.85	1.00				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194,072
+ 2% discontinuation rate (assumption 1)							
BSC	£117,409	2.95	0.90				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£191,953
+ treatment effect on hyperphagia (assumptions 1 + 2)							
BSC	£117,681	2.92	0.91				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£216,491
+ treatment effect on BMI-Z (assumptions 1 + 2 + 3)							
BSC	£117,559	2.81	0.91				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£231,190
+ 0.5 care-givers for adult patients (assumptions 1 + 2 + 3 + 4)							
BSC	£117,104	5.07	1.66				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£244,814
+ secondary care monitoring costs (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	£117,180	5.11	1.66				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£246,901

**Note incremental undiscounted QALYs calculated at a later date with a new simulation to the other results in the table, and so may differ within simulation error*

Table 25 Cost-effectiveness results for the EAGs preferred assumptions added incrementally and base case mixed 60% paediatric and 40% adult population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys base-case (probabilistic, updated model)							
BSC	£122,754	2.06	0.76				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£200,845
+ 2% discontinuation rate (assumption 1)							
BSC	£122,562	2.18	0.81				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£198,686
+ treatment effect on hyperphagia (assumptions 1 + 2)							
BSC	£122,773	2.13	0.78				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£223,265
+ treatment effect on BMI-Z (assumptions 1 + 2 + 3)							
BSC	£122,947	2.04	0.75				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£236,905
+ 0.5 care-givers for adult patients (assumptions 1 + 2 + 3 + 4)							
BSC	£123,223	4.21	1.61				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£251,527
+ secondary care monitoring costs (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	£122,781	4.24	1.63				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£251,669

The results from the probabilistic sensitivity analysis (PSA) based on 1000 iterations are displayed on the cost-effectiveness plane (Figure 9) and in a cost-effectiveness acceptability curve (CEAC) (Figure 10). The CEAC in Figure 10 shows that at a WTP value of £250,000, setmelanotide becomes more likely to be cost-effective than BSC. One-way deterministic sensitivity analyses for the EAGs preferred base-case are shown in Figure 11, which highlights the parameters with greatest impact on the ICER, and are in line with those identified in the companys updated base-case (Figure 8).

Figure 9 EAG's preferred base case probabilistic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide in paediatric patients with BBS (company's updated model)

Figure 10 EAG's preferred base case cost-effectiveness acceptability curve for the use of setmelanotide in paediatric patients (company's updated model)

Figure 11 One-way deterministic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide vs BSC in paediatric patients for EAG's preferred base case

Results for the EAGs preferred base-case in the adult BBS population are provided in Table 26.

Table 26 EAG's preferred base case probabilistic cost-effectiveness results in adult subgroup (updated CS model)

	setmelanotide	Best supportive care
Total cost	[redacted]	£131,391
Total life-years gained	[redacted]	20.71
Total quality-adjusted life years	[redacted]	1.54
Incremental costs	[redacted]	
Incremental life years gained	[redacted]	
Incremental undiscounted quality-adjusted life years*	[redacted]	
Incremental quality-adjusted life years	[redacted]	
Incremental cost-effectiveness ratio	£283,877/QALY	

**Note incremental undiscounted QALYs calculated at a later date with a new simulation to the other results in the table, and so may differ within simulation error*

6.4 Conclusions of the cost effectiveness section

Under the EAGs preferred base-case assumption, the ICER is £246,901 for setmelanotide plus BSC compared with BSC alone in a paediatric BBS population, and £283,877 for the adult BBS population. BBS is a rare condition, and so it is not surprising that there is a paucity of evidence on these patients with which to populate the model. Strong assumptions were made on several aspects of the model that had a big impact on the ICER, including the effect of treatment on hyperphagia, the long-term effects of setmelanotide on BMI-Z / BMI, the number of carers for adult patients, the source of utilities, and the utility multiplier for BBS patients due to non-obesity-related comorbidity. The company have restricted to the population with severe hyperphagia, however we note that the marketing authorisation doesn't restrict on hyperphagia, and our scenario including a mix of patients with moderate and severe hyperphagia had the largest increase on the ICER out of the scenarios we explored.

7 QALY Weighting

In the companys base-case the undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the EAG preferred base-case the undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). Whilst all these figures are uncertain and based on strong assumptions, the EAG considers that it is plausible that a QALY weighting between 1 to 3 may apply in the paediatric population. The EAGs base-case estimate would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

The company notes that obesity can also have financial implications for patients being associated with work absenteeism and presenteeism and permanent work loss. Also for children one parent may have to work part-time or even give up their job to provide care, plus additional costs associated with travelling to specialist BBS appointments at centres in Birmingham or London, plus spending more on food that other patient groups. In the companys original model they run a scenario including care-giver productivity costs which reduces the companys original base-case ICER from £191,759 to £179,295. The EAG agree that there are uncaptured costs, but the magnitude of these is uncertain.

The company also note that treating obesity in BBS patients may have other health benefits that it was not possible to capture in the model, such as making overall patient management easier and hence also easier to manage other co-morbidities related to BBS. Further there are additional comorbidities directly related to obesity not included in the model: dyslipidaemia, anxiety and depression, and polycystic ovary syndrome. The EAG agrees that there may be additional obesity comorbidities not captured, but the impact of these is uncertain.

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9 APPENDICES

9.1 Appendix 1

9.1.1 EAG critique of CS risk of bias assessment

The EAG's assessment of risk of bias was conducted by one reviewer and checked by a second (Table 27). Any disagreements were resolved by discussion. The EAG and CS risk of bias assessment using the NICE recommended tool were broadly similar. However, the EAG focused on outcomes at 14-weeks, as the tool used by the CS was for randomised studies and the 14-week endpoint is the only randomised outcome data. It is not clear what endpoint the CS considered, but answers to signalling question for intention to treat analyses discuss the 52-week outcomes. The EAG rated imbalances in dropouts and selective reporting domains differently to the CS:

- The EAG answered 'No' to the question 'Were there any unexpected imbalances in dropouts between groups' as only one patient in placebo group had dropped out at 14 weeks; and
- The EAG answered 'Yes' to the question 'Is there evidence to suggest that the authors measured more outcomes than they reported?' The EAG had concerns that QoL outcomes (PedsQL or EQ-5D) at 14 weeks are not reported in CS despite being collected and pre-specified in the protocol.

Table 27: Risk of Bias in RM-493-23 trial, for endpoints at 14 weeks, assessed by company and by EAG at trial level.

RoB assessment tool used in CS (overall trial assessment)			
Domain	**CS assessment**	**EAG assessment**	**EAG rationale / comment**
Was the randomisation method adequate?	Yes	Yes	"Patients assigned a unique randomisation number via an interactive website response system based on a randomisation code generated prior to the start of the study." No concerns.
Was allocation adequately concealed?	Yes	Probably yes	
Were groups similar at the outset of the study in terms of prognostic factors?	Yes	Probably yes	The groups were similar in baseline BMI. Any differences in patient characteristics between setmelanotide and placebo arms in CS [Table 12] are compatible with chance, given the sample size.
Were care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Patients, care providers and study stuff were all blinded (excluding analyst) for the duration of the 14-week placebo-controlled RCT. The blind (for the initial 14-week period) was maintained throughout the further 38 weeks of open-label single arm period that followed. However, unblinding

			is likely, especially in patients receiving setmelanotide as the treatment progressed, due to the characteristic hyperpigmentation of the skin (tanning) caused by the drug.
Were there any unexpected imbalances in drop-outs between groups?	Yes	No	"Only one patient discontinued therapy during the placebo-controlled period and that patient was randomized to placebo. The reason for discontinuation was adverse event (anaphylaxis) occurring while on placebo."
Is there evidence to suggest that the authors measured more outcomes than they reported?	No	Yes	QoL outcomes (PedsQL, IWQOL lite, EQ-5D) at 14 weeks are not reported in CS despite being pre-specified in the protocol and data collected. The company provided clarification that the dataset was too small to allow mapping of PedsQL or EQ-5D and VAS scores and did not allow for a separate analysis at 14 weeks. QoL outcomes at the end of the randomized period would be informative.
Did analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Probably yes	"There are no missing data in the 14 weeks outcome in the RM-493-023 trial, regardless of the treatment arm." "Comparison of setmelanotide- and placebo-treated patients after ~14 weeks was assessed using a sensitivity failure analysis, in which patients with missing 14-week data were considered treatment failures." These two statements contradict each other. The latter suggests there were missing outcomes which were imputed.
Overall	Not assessed	Some concerns	Exploratory QoL outcomes at 14-weeks have not been reported.

CS risk of bias assessments are reproduced from Table 20 of company submission.[14]

BBS=Bardet-Biedl syndrome, BMI=Body Mass Index, CS = company submission, EAG = External Assessment Group, FAS=full analysis set (as defined in company submission), RCT = randomised controlled trial; RoB = Risk of Bias, QoL=quality of life; PedsQL= Paediatric Quality of Life Inventory, IWQOL lite= Impact of Weight on Quality-of-Life Questionnaire-Lite; VAS= visual analogue scale

9.2 Appendix 2

9.2.1 Systematic review of clinical effectiveness

The EAG conducted an appraisal of the CS systematic literature review using the ROBIS tool[17]. The completed ROBIS checklist is in section 9.2.2. The concerns noted by the EAG are described in sections 9.2.1.1 to 9.2.1.3 below.

9.2.1.1 Study reports published after the date of the last search in the CS SLR:

Two key publications were published after the date of the last search (August 2022).[1, 13] One further report appears to be a conference contribution[18] for which a published abstract is available but not included in the SLR. Whilst we acknowledge that the company were aware of, and will have had access to their trials and study data (so were able to complete their submission), the systematic review fails to account for these 'unpublished' reports and is, therefore, incomplete.

Haqq AM, Chung WK, Dollfus H, Haws RM, Martos-Moreno G, Poitou C*, et al.* Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes & endocrinology* 2022;**10**(12)[13]

This is the main trial report for RM-493-023 and was E-published on Nov 7 2022: The report was listed as an addendum to the SLR. However, it is unclear if it was integrated into the systematic review in terms of review process and appraisal.

Forsythe E, Haws RM, Argente J, Beales P, Martos-Moreno G, Dollfus H*, et al.* Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results. *Orphanet J Rare Dis* 2023;**18**(1)[1]

This publication focuses on the Health-Related Quality of Life data from RM-493-023. The CS includes a reference to an earlier poster presentation of this publication (Forsythe 2021) but they do not acknowledge this journal publication which was published on Jan 16 2023.

Argente J, Clement K, Chung WK, et al. Long-term efficacy of setmelanotide in patients with Bardet-Biedl syndrome. Endocrine Society annual meeting June 2022; Atlanta, GA[18]

Argente 2022 is described in Table 7 of the CS as being the main publication for RM-493-022. In addition to the conference details listed in the SLR, the following abstract was identified by the EAG with a publication date of November 1 2022: Argente *et al*, ODP606 Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome, Journal of the Endocrine Society, Volume 6, Issue Supplement_1, November-December 2022, Page A14.

9.2.1.2 SLR inclusion criteria for outcomes broadly defined.

The outcomes of the review were classified broadly as 'efficacy' or 'safety'. The EAG consider that good practice for systematic reviews of clinical effectiveness requires outcomes to be specifically and clearly defined.[52] Otherwise there is a risk of inconsistent inclusion and extraction between reviewers, and external validation and repetition of the process is challenged. Moreover, there is the possibility of selective outcome reporting ('cherry picking') which would introduce bias into the review. The outcomes for the SLR of clinical effectiveness should have been explicitly listed and defined (e.g., reduction in body weight, etc.,) with examples of outcome measurement (e.g., >10% by any measurement kgs, lbs etc).

9.2.1.3 Approach to data extraction

The company SLR prioritised data extraction from published papers with the longest follow-up. There are four concerns the EAG highlights with this approach:

- As noted above, the SLR searches missed key journal publications. It is unclear how the company have dealt with this issue, given that their method of data extraction favoured published studies,
- Risk of publication bias: where the company have focused on published reports over unpublished or grey literature,
- Data for earlier time-points may have been omitted in extraction, and therefore not reported in the CS (as published papers with the longest follow-up were prioritised), and
- The company do not report in their protocol how they have missing data was handled.

9.2.2 Completed ROBIS checklist for company SLR of clinical effectiveness studies.

The EAG's ROBIS assessment was conducted by one reviewer and checked by a second. Any disagreements were resolved by discussion. ROBIS Key for judgements: (Y = Yes; N = No; PY= Probably Yes; PN = Probably No; NI = No Information)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA

Objectives: "*The objective of this project is to conduct an SLR on the burden of BBS-related obesity. This SLR will collate and synthesize evidence in the literature regarding the clinical efficacy and safety of interventions for the treatment of obesity in patients with BBS".* (CS, Appendix D. Page 1)

Table 16: PICOS selection criteria (CS, Appendix D. Page 9)

Domain	Inclusion	Exclusion Criteria
Population	Paediatrics and adults with obesity or hyperphagia caused by BBS plus, the following obesity markers: • Adults aged 18 years and over: BMI >30 kg/m • Paediatrics aged ≤17: weight ≥97th percentile for age on growth chart assessment or BMI z-score ≥+2SD for	• Patients ages under 6 years old • Patients with obesity due to other genetic deficiencies or syndromes, or those not meeting the age-specified obesity markers • Mixed populations of patients of interest plus patients not of

	children ages 5–19, ≥+3SD for children under 5	interest without results reported separately
Intervention/ Comparator	Interventions for the treatment of obesity/ hyperphagia*	Interventions not intended to treatment obesity and/or hyperphagia
Outcomes	• Efficacy or safety outcomes reported from real-world treatment studies Efficacy and safety outcomes reported from clinical trials	Studies that do not report any outcomes of interest
Study design	• Observational real-world evidence study reporting treatment outcomes Any clinical trial investigating the efficacy and safety of treatment	Case studies/case series Letters to the editor, editorials, comments, opinions, notes, narrative reviews SLR/meta-analysis/network meta-analysis published in 2018 or earlier

1. Did the review adhere to pre-defined objectives and eligibility criteria?	Y
2. Were the eligibility criteria appropriate for the scope?	Y
3. Were eligibility criteria unambiguous?	PY
4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	PY
5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y
	Low

Rationale: A protocol for the SLR was provided. The EAG have some concerns regarding the specification of broad eligibility criteria for outcomes.

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES

Studies were identified for all three reviews (clinical, economic, quality of life) reported in the submission via one search. The EAG consider this to be a suitable approach. Searches were undertaken in June 2021 and updated in August 2022.

Bibliographic databases searched included:

- Embase (Ovid)
- MEDLINE (Ovid)
- The Cochrane Library (Ovid)
- DARE (Ovid)
- PsycINFO (Ovid)
- Econlit (Ovid)
- DARE/NHS EED (CRD interface)

Clinical trials registry resources included:

- ClinicalTrials.gov
- Clinicaltrialsregister.eu

- Orpha.net

Conference meeting abstracts, identified by searches of Embase or via handsearching, included:

- European Congress of Endocrinology (handsearched)
- European Conference on Rare Disease and Orphan Products (Embase)
- Endocrine Society annual meeting (handsearched)
- European Congress on Obesity (2020 handsearched,. 2019, 2021-2022 via Embase)
- American Association of Clinical Endocrinologists annual congress (2019-2020 handsearched, 2021-2022 Embase)
- European Society for Paediatric Endocrinology (2021-2022 Embase)
- Pediatric Endocrine Society (2021-2022 Embase)
- The Obesity Society (2021-2022 Embase)
- American College of Medical Genetics (2021-2022 Embase)

Studies were selected independently by two trained researchers with access to a third researcher in the event of any disagreement.

1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y
2. Were methods additional to database searching used to identify relevant reports?	Y
3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y
4. Were restrictions based on date, publication format, or language appropriate?	Y
5. Were efforts made to minimise error in selection of studies?	Y
	Unclear

Rationale for concern: The approach to, and conduct of, the searching was of good quality. Studies were selected in-line with guidance.

The EAG note, however, that the date of last search (August 2022) means that primary reports for RM-493-023 have been omitted in the searches. This means that the primary and complete report of RM-493-023 has not been included in the review.

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL

Data Extraction: Data were extracted by one researcher and independently checked by a second senior researcher.

Study Appraisal: the company appraised Risk of Bias using the minimum criteria specified in PMG24 for the main trial and the open-label extension.

1. Were efforts made to minimise error in data collection?	Y
2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PN
3. Were all relevant study results collected for use in the synthesis?	N
4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y
5. Were efforts made to minimise error in risk of bias assessment?	NI

	High

Rationale:

Data extraction: The process reported aligns with guidance but there are concerns about how data were extracted:

'For studies with multiple publications, the most recent results, records with the longest follow-up period, or results reported in a primary full-text publication were extracted and summarised.' (CS, Appendix D. Page 10)

Best practice is to extract all reports into one extraction spreadsheet, irrespective of date of publication, length of follow-up, or publication status. This ensures all data are captured and considered for analysis and it allows for inter-report checking for any discrepancies or typographical errors.

Our concern is the possibility that not all reports have been considered or appraised and that their approach introduces publication bias in reporting where published reports are favoured. We appreciate that the risk here is low, given the limited number of studies and lack of any pooled analysis, but the deviation from best practice raises concern about conduct and completeness. This linked to concerns about reporting and data use throughout the submission.

Critical Appraisal: The company do not report their process (conduct) for assessing risk of bias, so we are unable to appraise if this was suitable (we report NI above). The EAG have critiqued the appraisal reported in the submission above (3.2.5.2Efficacy outcomes and risk of bias assessment). EAG preference is the RoB 2 tool, for RCTs, and ROBINS-I for the non-randomised studies. As the company SLR was not specific is eligibility for outcomes, a transparent evaluation of methods of bias assessment is challenging.

DOMAIN 4: SYNTHESIS AND FINDINGS	
1. Did the synthesis include all studies that it should?	Y
2. Were all pre-defined analyses reported or departures explained?	Y
3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y
4. Was between-study variation minimal or addressed in the synthesis?	N/A
5. Were findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	N/A
6. Were biases in primary studies minimal or addressed in the synthesis?	PN
	Unclear

Rationale: Although the signalling questions for this domain would indicate a low rating, the EAG note that the full SLR and protocols were not initially provided as part of the submission and had to be requested. The protocols were only provided in the late stages of the appraisal. The review identified all of the eligible studies, but eligible reports were missed by the searches. The company could have included unpublished, pre-publication reports in their submission, and updated their review accordingly. The EAG cannot rule out the possibility of selective reporting in the CS since they did not match pre-specified analyses in the CS or clarification letter (see 3.4.2)

9.3 Appendix 3: Mapping from PedsQL to EQ-5D in BBS paediatric population

Forsythe 2023 reports a mean (SD) PedsQL total score for BBS children at baseline of 67.2 (18.9), and an improvement at 12-months of Setmelatonide of +11.2 (14.3).

In a study of children with inborn errors of metabolism (IEMs), such as hyperammonaemic disorders (HA), a different serious genetic metabolic disease, in four UK metabolic disease hospital clinics published in a conference abstract[53] and with additional data obtained from authors, PedsQL scores for children of similar baseline HRQoL were mapped onto utilities used Khan's 2014 algorithm models 6 (adjusting for age and sex, table reproduced below in Table 28).

Table 28 Results from mapping age-appropriate PedsQL scores for patients with hyperammonaemic disorders

PedsQL instrument	n	Mean PedsQL score	SD	Mean EQ-5D score	SD
Young Child aged 5-7	13	65	22	0.75	0.26
Child aged 8-12	33	66	21	0.73	0.22
Teenager aged 13-18	40	70	21	0.77	0.22
Young Adult aged 18-25	5	88	17	0.91	0.10
All sample	91	69	21	0.76	0.22

When comparing patients with HAs (n=45, 53% females, mean age [SD] 12.7 [5.4]) years) with patients without HAs but other IEMs (n=46, 43% females, mean age [SD] 12.9 [3.5]), mean (SD) PedsQL scores were 63 (24) and 74(16), again an 11 point mean difference in PedsQL scores as observed in Forsythe 2023 and at a similar range in the scale, albeit slightly lower. These PedsQL scores corresponded to utility values of 0.70 (SD= 0.26) and 0.82 (SD=0.14), or 0.12 utility points difference in the raw scale, or 0.146 difference (95%CI -0.23, -0.06) when adjusting for age, sex, and hospital.

Transposing these mapped utility scores from the IEM population to the BBS child population in Forsythe 2023, a baseline PedsQL score of 67.2 would correspond to utility weight between 0.73-0.77. We could apply an interpolation of utility scores for the remaining BMI-Z categories and an improvement of 0.12 or 0.145 QALYs to the effect of setmelanotide of reducing a mean 0.7 points in the BMI-Z score, as reported in Forsythe 2023. Using these utility estimates the EAG scenario would no longer require adjustments for hyperphagia and BBS multipliers for paediatric utilities in the model.

Unfortunately, there are no known mapping algorithms for the adult population for the IWQoL scores and data from the EQ-5D or the SF-12 and SF-36 questionnaires collected for the adult population in the RM-493-023 were not made available to the EAG. We could have applied a triangulation of methods to map SF-12 or SF-36 scores to EQ-5D utilities or

triangulate them with IWQoL scores, [50, 51] as done in other models for weight technologies.[54] Without these data, as patients in the model move from children to adults, we would again require data from Alsumali 2018 study, [21] weighted by the hyperphagia multiplier, with additional complexity to the model, and have therefore not pursued this change in the model.

EAG Response to factual accuracy check and confidential information check

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome – Factual accuracy check of the EAG report produced by the Bristol TAG (23 Mar 2023)

Page	Section	Inaccuracy	Correction	EAG Response
15	1.4 Key issue 3	The information requested in clarification questions A16 and A17 could be provided for the EAG to evaluate	Response to A17 was provided and is included below: *"There are no missing data in the 14 weeks outcome in the RM-493-023 trial, regardless of the treatment arm. Only one patient discontinued therapy during the placebo-controlled period and that patient was randomised to placebo. The reason for discontinuation was adverse event (anaphylaxis) occurring while on placebo.* *Thus, there is no answer to the question on the imputation model."*	We thank the company for providing clarification to question A17 but note that it was a two-part clarification – asking for both 14 and 52-week data - and the company response related to the 14-week data only. In addition, the company were not able to provide a response to clarification A16. A16 requested the patient characteristics for the imputed and non-imputed patients at 52-weeks. As such, we do not think what we have written is a factual inaccuracy. However, we have edited the text for Key Issue 3 to clarify that the statement relates to 52-week data only.
24	2.1 Second paragraph	72% to 93 % of people with BBS will be affected by obesity	Typo - 93% should be 92% (Forsythe 2018).	This has been corrected.
25	3 First paragraph	However, the company also states there are no ongoing studies (CS, section B.2.11), which appears to contradict ClinicalTrials.gov, which reports an estimated study	• Although technically correct, study RM-493-022 is ongoing, please note that this is a basket study of treatment with setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, and includes patients with other conditions not solely for BBS	We have reworded this sentence to read: "In the factual accuracy response, the company noted that, although the study is ongoing, as reported on ClinicalTrials.gov, most BBS patients are no longer in the study

		completion date of December 2023.	patients. Most BBS patients are no longer in the study and no new data output is anticipated for BBS patients from this study. Hence, why it was reported that there are no ongoing studies for BBS. • Typo. Should read December 2024 https://clinicaltrials.gov/ct2/show/NCT03651765	and no new data output is anticipated for BBS patients from this study." The typo is no longer in the text.
28	3 Table 3 – Outcomes row, EAG comments column	The EAG also note that: percent body fat, waist circumference, incidence of T2DM...	Percent body fat and waist circumference were reported in section B.2.6.1.4, incl. tables 36 and 37, respectively (p 81 of the CS v2).	The EAG has checked tables 36 and 37 in the CS and agree with the company. We have removed percent body fat and waist circumference as outcomes not directly reported on in the CS.
32	3.2.1 Table 4	In their tabular overview of clinical evidence the EAG have missed a key outcome	The following outcome should be included in the table: Proportion of patients aged ≥18 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks – post hoc – single arm (no comparator - trial RM493-023 company submission (Table 23).	Thank you. This outcome has now been added to Table 4.
37	3.2.5.1 End of first paragraph	However, it is not clear that all 'pivotal' participants were included in analyses at 52 weeks, as claimed on page 56 of the CS (section B.2.4).	Typo in page number, should be p55 of v2 of CS.	This has been corrected.
38	3.2.5.1 Last paragraph	However, the CS also reports a post hoc subgroup analysis of BBS patients aged ≥18 years. It is not explicitly stated if this was for the purposes of the submission, nor if the analysis was intended	While technically correct, the CS does state on p66 (section 2.6.1) that: *"Results throughout this section are presented separately for patients aged ≥18 years and those aged <18 years. In growing children, body weight is heavily influenced by physical development and maturation. Body weight is, therefore, primarily used for patients aged ≥18 years, whilst weight-related parameters that account for differences in height (such as BMI) and those that account for differences in age*	We have deleted the 2nd sentence so this now reads: "However, the CS also reports a post hoc subgroup analysis of BBS patients aged ≥18 years."

		to address the requirements of the NICE scope	*and sex (such as BMI Z score and the percentage of the BMI 95th percentile score) are used for patients aged <18 years."*	
42	3.2.5.2.1 Table 8	Estimated proportion of patients aged ≥18 years achieved a ≥10% reduction in body weight after 52 weeks was [redacted] (n=15) (Table 23 of the CS).	The values are no longer academic in confidence in v2 of the CS.	
43	3.2.5.2.1 Table 8	Mean percent change in body weight was described in all patients (pivotal and supplemental) aged ≥18 years. A reduction in body weight from placebo-controlled period baseline to 14 weeks was shown in the setmelanotide treatment arm (n=10), when compared to the placebo arm (n=12). Mean percent change (kg) in the setmelanotide arm after 14 weeks was [redacted] versus [redacted] in the placebo arm [redacted]	Table 25 reports [redacted]. The p value stated here by the EAG is for change after 14 weeks, not percent change after 14 weeks.	Thank you for picking this up. This has now been amended.
51	3.2.6	HRQoL data from RM-493-023 were also	The HRQoL data reported in the Forsythe paper are for all patients who completed the QoL questionnaires	The EAG has now reworded this sentence with the deletion of 'for responders':

	First paragraph	published in a separate paper by Forsythe *et al* [1] for responders	(randomized patients who received ≥1 dose of setmelanotide or placebo and have baseline and Week 52 data), not just for responders to setmelanotide.	"HRQoL data from RM-493-023 were also published in a separate paper by Forsythe *et al* [1]"
52	3.2.6 First paragraph	However, data for PedsQL were not presented in the CS	Effect of setmelanotide on PedsQL score in BBS patients aged <18 years without cognitive impairment who provided baseline and Week 52 data is reported in table 40 of the CS.	The EAG have now amended the text by deleting this sentence from the paragraph.
54	3.4 First paragraph	However, this is based on an assumption that all 'responders' from the main study (RM-493-023) had severe hyperphagia at baseline	This is an incorrect interpretation of the assumption. The assumption is that in real life, patients likely to be treated with setmelanotide are those with severe hyperphagia.	We do not think what we have written is a factual inaccuracy. In clarification response A1, the company states the following: "It was instead assumed that any patients who responded to setmelanotide, in terms of seeing a clinically meaningful reduction in weight/BMI/BMI-z over the duration of the trial, had entered the trials with severe hyperphagia (the severe hyperphagia being the cause of their obesity) and that the weight response to setmelanotide was mediated through a reduction in hyperphagia severity."
63	4.2.6.1 First paragraph	The proportion of paediatric patients who respond to treatment at 14 weeks in the model was estimated to be [redacted] (CS Table 31), based on the proportion of paediatric patients achieving a BMI Z score reduction of ≥0.2 after 52 weeks	• The response rates are no longer academic in confidence in CS v2. • > 10% weight loss should be ≥ 10% weight loss.	Thank you. This has been corrected, and the confidentiality marking updated.

		of setmelanotide from Study RM-493-023 (pivotal patient FAS). For adults a [redacted] response rate is assumed based on the proportion of adult patients with >10% weight loss (CS Table 23) from Study RM-493-023 (pivotal patient FAS).		
88	7 Last paragraph	The company also note that treating obesity in BBS patients may have other health benefits that have not been captured in the model, such as making it easier to manage other co-morbidities related to BBS.	This should be: The company also note that treating obesity and hyperphagia in BBS patients may have.... The full statement in the CS (p 153) is: *"Treating obesity in BBS patients may also have other health benefits that it has not been possible to quantify in the model. Treating the hyperphagia and obesity may make the overall patient management easier and thus the management of other co-morbidities related to BBS."*	We have re-worded this to: "The company also note that treating obesity in BBS patients may have other health benefits that it was not possible to capture in the model, such as making overall patient management easier and hence also easier to manage other co-morbidities related to BBS."
96	9.2.2 Table 16	Paediatrics aged ≥17	Typo – it should be Paediatrics aged ≤17.	This has been corrected.

Highly Specialised Technology

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome ID3947

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **05 June 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Rhythm Pharmaceuticals
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	We, Rhythm Pharmaceuticals do not have past or current, direct or indirect links to, or funding from, the tobacco industry

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue #1: In the absence of a validated measure of hyperphagia, how will Bardet-Biedl syndrome patients with severe hyperphagia be identified in clinical practice?	No	The submission covers BBS patients with severe hyperphagia, as consultation with BBS experts identified that these patients will be those who would most benefit from therapy with setmelanotide. These patients experience an overwhelming, heightened, and relentless hunger that mimics feelings of starvation and results in excessive food consumption and a preoccupation with food that interferes with a patient's ability to function in daily life. The result of severe hyperphagia is early onset severe obesity, often occurring by the age of 5 years. BBS patients are treated at specialist BBS centres by clinicians experienced in the diagnosis and management of BBS, and who use their expert judgement to identify and assess hyperphagia. BBS experts can and will identify severe hyperphagia through careful questioning of the patient and / or caregiver and based on the patient history. Indicators clinicians will look for include: ▸ Patient reporting that they are continuously hungry, even despite recent food intake ▸ Patient overeating at meals and eating constantly, including several times during the night

		▸ Caregivers having difficulty managing the patient's eating habits and having to hide / ration food ▸ Patient experiencing distress or inappropriate behavioural response if denied food ▸ Patient having rapid or continued weight gain despite diet and exercise regimen In the vignette study conducted by Rhythm Pharmaceuticals, severe hyperphagia was described in terms of subjective experience, observable behaviours and its impact as described below, reflecting the indicators clinicians will look for in their assessment of hyperphagia severity: **Subjective Experience** • You **almost never feel full** after a **normally sized meal** • You become **hungry again almost immediately** after eating a meal • Thinking about food **almost always interferes** with your **normal activities** of daily living **Observable Behaviors** • You overeat to the point of **discomfort at most meals** • You eat **almost constantly** • You eat during the **hour** before you go to bed **almost every night** • You **eat** a large number of calories when you wake up **during the night almost every night** • You try to **sneak food** without people knowing **almost every day** **Impact** • You become **extremely distressed or upset** when **denied food**

		• Because of hunger and eating behavior, you have **severe problems performing daily activities** such as self-care, getting around, leisure activities and work or school • Because of hunger and eating behavior, you have **severe problems with your relationships** with family and friends In the RM-493-023 and RM-493-022 clinical studies hyperphagia was not measured because no tool exists for measuring hyperphagia that is specific for BBS patients. The Dyken's hyperphagia questionnaire developed for Prader-Willi syndrome (PWS) was not considered appropriate for the studies because it is a caregiver-reported instrument since patients with PWS are unable to reliably self-report (Fehnel et al. 2015) and thus would not capture the personal and subjective nature of hyperphagia which is critical in BBS. While patients with BBS have severe hyperphagic behaviours, these behaviours don't completely align with those found in PWS (and therefore measured by Dyken's). *Fehnel et al. 2015. Development of the Hyperphagia Questionnaire for Use in Prader-Willi Syndrome Clinical Trials. Presented at: ISPOR 20th Annual International Meeting*
Key issue #2: Are the findings of studies RM-493-023 and RM-493-022 generalisable to NHS practice?	No	The studies were conducted in the US, Canada, the UK, France, and Spain, most patients being from the US. In terms of ethnicity, in study RM-493-023 77.3% of patients where white, and in study RM-493-022, 86.7% of patients were white. The Office of National Statistics states that in 2021 in England and Wales, 81.7% of the population identified as white. It is therefore reasonable to assume that the data from the setmelanotide trials can be considered generalisable to the UK decision making context. We note in the attached engagement papers that the British Obesity and Metabolic Surgery Society (BOMSS) submission states in their response to question 18, that the clinical trials on setmelanotide reflect current UK clinical practice.

		We acknowledge the EAG's suggestion of using the CRIBBS registry to characterise the UK based BBS patient population and have taken this into consideration. However, the number of UK patients [redacted] in the CRIBBS registry is not enough to characterise the UK BBS population. Furthermore, only a subset of CRIBBS patients have reliable longitudinal data on weight gain and the sample used for definition of the null hypothesis, following recommendation of regulatory authorities, does not detail the country of origin of patients.
Key issue #3: How reliable and valid are the clinical effectiveness results for key outcomes reported by RM-493-023?	Yes	A response to clarification question A17 was provided. The clinical study report was shared with the EAG in response to the EAG report factual accuracy check and includes information on the multiple imputation approach used for the different outcome, including the number of patients for whom data was imputed for different outcome. The baseline characteristics for participants whose follow-up data at 52 weeks was imputed and for participants whose follow up data was not imputed, requested in clarification question A16 are provided with our response (Appendix A). We also now provide additional information on the number and proportion of patients for whom data was imputed for key endpoints at week 52 (Appendix B).
Key issue #4: What is the impact of potential bias arising from absence of randomised, controlled comparisons for key clinical outcomes at 52 weeks follow-up in RM-493-023?	No	BBS is a rare disease making traditional comparative clinical studies a great challenge. Strong phase II data which showed that 70% of patients achieved a ≥5% weight loss at 3 months, informed the study design. The design of the Phase III was chosen based on discussions with regulatory authorities and clinical study investigators to optimise patient retention in the study, maximise patient exposure to active therapy and minimise the risk of unblinding due to the impact on hyperphagia and to hyperpigmentation. Advice from clinical study investigators indicated that patients would be reluctant to continue daily subcutaneous injections for 52 weeks without experiencing any clinical effect. We also acknowledge a small, negligible initial placebo effect, but we believe that this effect remains constant until week 52, and thus we do not believe this placebo effect shows an apparent regression to the mean.

		Hunger scores, BMI, BMI-Z and weight remained virtually unchanged for patients on placebo during the initial 14-week treatment phase, and hence would not require adjusting for. This is supported by studies with semaglutide (STEP 1, STEP 5 and STEP TEENS) which also show that the placebo response plateaus around week 16. Though note that the semaglutide studies include active lifestyle intervention in both arms, which may contribute to a larger effect in the placebo arm. By comparison hunger scores, BMI, BMI-Z and weight are significantly reduced during the first 14 weeks of setmelanotide treatment. The figures presented in response to clarification question A15 and figure 6 of the CS show that from 14 weeks all patients are on setmelanotide, and that patients initially randomised to placebo then start experiencing a reduction in hunger scores weight / BMI / BMI-z with the curves of the two arms merging around week 24.
Key issue #5: To what extent does the selective outcome reporting of exploratory outcomes reduce confidence in clinical effectiveness and cost-effectiveness results?	Yes	All relevant outcomes were reported. Study reports have since been shared as response to the EAG report factual accuracy check as requested by the EAG. Table 7 of the RM-493-023 study report (file 2.4.1.2.25 rm-493-023-body) lists all the protocol amendments, incl. dates and substantive changes. The last amendment was implemented on 9th September 2020, which was before the first data readouts. The first efficacy analyses for the CSR and for publication were carried out on 24th of May 2021, i.e. after the last protocol amendment was implemented. Prior to that a safety analysis was carried out in October 2019, but this was limited to safety outcomes. We also now share the updated study protocol for study RM-493-023 (Appendix C) as requested as well as PedsQL and IWQOL data for this study (Appendix D and F). Nevertheless, HRQoL data collected in study RM-493-023 are not appropriate to determine QALYs for the following reasons: • EQ-5D is not sufficiently sensitive to pick up effects on hyperphagia. The company submission included the rationale for this (that hyperphagia is not a domain that is covered by EQ-5D and therefore it will miss the impacts of

		treatment on hyperphagia.) This is similar to other disease areas/conditions where EQ-5D is known to be insensitive, such as insomnia, fatigue, blindness, and deafness. For this reason, utility estimates were estimated through using a vignette study and the EAG accepted this rationale.
		• Notwithstanding this, the PedsQL dataset was too small to allow mapping onto EQ-5D and VAS scores and did not allow separate analysis at 14 and 52 weeks.
		  ○ Few patient data available at week 52 (3 patients without cognitive impairment, 6 with cognitive impairment)
		  ○ Effect of setmelanotide at 14 weeks would have been too small to be captured by the tools
		• As noted by the EAG in their report, there are no known mapping algorithms for IWQOL scores
		• Furthermore, IWQOL and PedsQL do not include domains that would sufficiently capture the impact of hyperphagia and hence mapping these to EQ-5D would not improve the uncertainty of the hyperphagia utility and thus would not improve uncertainty of the ICER.
		• SF-36 and SF-10 like IWQOL and PedsQL do not include domains that would sufficiently capture the impact of hyperphagia and hence mapping these to EQ-5D would not improve the uncertainty of the ICER. Also, the EAG acknowledge in their report that using SF-36 would result in additional complexity to the model and did not pursue this change in the model.

Key issue #6: All responders are assumed to move to the mild hyperphagia state, independent of change in BMI-Z / BMI.	Yes	The EAG used in their base case an alternative scenario where responders can move either to moderate or mild hyperphagia state with the proportions in each state based on the proportion of responders who have a 1 or 2 class reduction in BMI-Z. This is based on the assumption that patients who experienced BMI-Z reduction of 1 class had moved to moderate hyperphagia and that patients who experienced 2 class reduction moved to mild hyperphagia.

		While we understand the rationale, we do not agree with it, for the following reasons: • To be considered a responder to setmelanotide treatment, patients need to attain significant sustained change in BMI-Z over one year. To achieve this, patients need to experience a substantial change in eating habits which can only be brought about by experiencing mild hyperphagia, as moderate hyperphagia would not yield the observed reduction in BMI-Z. See below definition of moderate and mild hyperphagia. Thus, a 1 class reduction in BMI-z does not indicate a move to moderate hyperphagia instead of mild hyperphagia; it indicates a slower change in eating habits. • The impact on BMI-Z is not a reliable proxy for impact on hyperphagia, as the benefits from hyperphagia reduction go beyond those reflected by weight loss and include impact on quality of life due to the reduction in hunger, improvement in eating habits and disruption of sleep, mood and emotions, leisure activities, and relationships with friends and family. • Clinical experts in BBS agree that when treated with setmelanotide obese BBS patients' with severe hyperphagia at baseline change from severe to mild, independently of the magnitude of weight lost. • The 1 class reduction in BMI-Z is an underestimation of the effect on BMI-Z on these patients because of the limitations of the lower and upper BMI-Z score class ranges which are less sensitive to changes in BMI-Z. o The BMI-Z score classes defined in the study were <1, 1 to <2, 2 to <2.5, 2.5 to <3, 3 to < 3.5, 3.5 to <4, >4, i.e., at the extremities the range in BMI-Z is greater than the 0.5 ranges in the middle classes. o There were [redacted] patients with baseline BMI-Z >4 (some much greater than 4) and [redacted] with baseline BMI-Z [redacted]. If classes at the extremities had a range of 0.5 (as the classes between 2 and 4), then for patients with BMI-Z >4, [redacted] would have experienced a [redacted] reduction in BMI-Z, [redacted] patients would have experienced a [redacted] reduction in BMI-Z and [redacted] would have experienced a

		[redacted] reduction. The [redacted] with baseline BMI-Z [redacted] points in BMI-Z and was no longer obese, which would correspond to a [redacted] reduction. Based on classes being defined by increments in 0.5 BMI-Z scores, the mean shift in classes is [redacted], which is closer to 2 than 1. ○ Furthermore, the mean difference in BMI-Z score from baseline is [redacted] which corresponds to [redacted] class change ([redacted]/0.5), again nearer to a 2-class shift than a 1-class shift. Please refer to new evidence document Appendix E. Thus, we maintain that a 2-class change better reflects the impact on BMI-Z experienced by patients. ○ The choice of the class ranges was based on availability of published data to estimate the risk of comorbidities and the disutility of obesity. • The assumptions for hyperphagia transitions used in our base case are conservative, as we have not assumed any transitions occurred to no hyperphagia state. **MODERATE HYPERPHAGIA** **Subjective Experience** • You **usually do not feel full** after a **normally sized meal** • You become **hungry again within 1 hour** after eating a meal • Thinking about food **often interferes** with your **normal activities** of daily living **Observable Behaviors** • You **often** overeat to the point of **discomfort** • You eat **more than 3 meals** per day with **more than 3 snacks** • You **often** eat during the **hour** before you go to bed • You **eat** a large number of calories when you wake up **during the night about 2-3 times per week** • You try to **sneak food** without people knowing about **twice per week**

		Impact • You become **moderately distressed or upset** when **denied food** • Because of hunger and eating behaviour, you have **moderate problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behaviour, you have **moderate problems with your relationships** with family and friends **MILD HYPERPHAGIA** **Subjective Experience** • You **sometimes do not feel full** after a **normally sized meal** • You become **hungry again within 2 hours** after eating a meal • Thinking about food **sometimes interferes** with your **normal activities** of daily living **Observable Behaviors** • You **sometimes** overeat to the point of **discomfort** • You eat **3 meals** per day with **more than 2 snacks** • You **sometimes** eat during the **hour** before you go to bed • You **eat** when you wake up **during the night about once per week** • You **occasionally** try to **sneak food** without people knowing **Impact** • You become **mildly distressed or upset** when **denied food** • Because of hunger and eating behaviour, you have **slight problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behaviour, you have **slight problems with your relationships** with family and friends Regarding the request for further data to enable mapping between hunger score and hyperphagia state, no further data is available. Also, because there is a

		multifactorial correlation between hunger and hyperphagia, using extent of hunger in isolation is not an effective means of measuring hyperphagia.
Key issue #7: Size of the treatment effect on BMI-Z in responders to setmelanotide in the paediatric population uncertain	Yes	The EAG noted that there is variability in movement between BMI-Z classes in patients in study RM-493-023 and felt this was consistent with a 1-class reduction in BMI-Z instead of our assumed 2-class reduction. The EAG suggested that we use a standard distribution to estimate the treatment effect instead of using the current approach. Indeed, if we take the baseline mean and assume a normal distribution with standard deviation equal to the baseline SD, then we can calculate the expected proportion of patients falling into each BMI-Z category after treatment response. However, this would require altering the structure of the model which we do not believe is necessary as the current approach is not unreasonable. As explained for key issue #6, the 1 class reduction in BMI-Z is an underestimation of the effect on BMI-Z on these patients because of the limitations of the lower and upper BMI-Z score class ranges which are less sensitive to changes in BMI-Z. • The BMI-Z score classes defined in the study were <1, 1 to <2, 2 to <2.5, 2.5 to <3, 3 to < 3.5, 3.5 to <4, >4, i.e., at the extremities the range in BMI-Z is greater than the 0.5 ranges in the middle classes. • There were [redacted] patients with baseline BMI-Z >4 (some much greater than 4) and [redacted] with baseline BMI-Z [redacted] If classes at the extremities had a range of 0.5 (as the classes between 2 and 4), then for patients with BMI-Z >4, [redacted] would have experienced a [redacted] reduction in BMI-Z [redacted] patients would have experienced a [redacted] reduction in BMI-Z and [redacted] would have experienced a [redacted] reduction. The [redacted] with baseline BMI-Z [redacted] points in BMI-Z and was no longer obese, which would correspond to a [redacted] reduction. Based on classes being defined by increments in 0.5 BMI-Z scores, the mean shift in classes is [redacted], which is closer to 2 than 1. • Furthermore, the mean difference in BMI-Z score from baseline is [redacted], which corresponds to [redacted] class change ([redacted]/0.5), again nearer to a 2-class

		shift than a 1-class shift. Please refer to Appendix E. Thus, we maintain that a 2-class change better reflects the impact on BMI-Z experienced by patients. • The choice of the class ranges was based on availability of published data to estimate the risk of comorbidities and the disutility of obesity. We believe that the paediatric data show consistency of reduction in BMI-Z and consistency in clinical benefits for the patients and that using a reduction of 2 classes on average is a fair representation of change in that population and a valid hypothesis for the model. Furthermore, in clinical practice which will involve multidisciplinary care including the management of obesity (incl. active management of diet and exercise), the effect of hyperphagia reduction on BMI-Z in patients treated with setmelanotide is anticipated to be greater than that observed in the clinical trial, in which changes to diet and exercise were not allowed.
Key issue #8: BMI-Z / BMI reduction is extrapolated into the long-term	No	While the EAG do acknowledge in their report that the evidence for GLP-1 receptor agonists show only a small waning of treatment effect at 104 weeks compared with 52, suggesting that interventions that act on hunger have the potential to achieve sustained effects in the short to medium term, in their base case the EAG assume 1% patients per year return to their original BMI/ BMI-Z. We do not agree with this assumption, as in patients who respond to setmelanotide the hyperphagia benefit is retained, with the consequent change in eating habits and thus patients experience a benefit in BMI/BMI-Z which they would not experience if they were not on setmelanotide. Patients with severe hyperphagia who are untreated are on an ever increasing weight trajectory, hence when treated with setmelanotide even if an increase in BMI/BMI-Z can be observed in the long term, the benefit is retained compared to the BMI/BMI-z the patient would have achieved if left untreated. Note that in our base case the model is conservative, as: • It does not account for increase in BMI/ BMI-Z in patients with severe hyperphagia not treated with setmelanotide.

		• Patients who stop setmelanotide treatment revert back to their baseline BMI/BMI-Z score category immediately, with no tapering of treatment effect, i.e., without accounting for the benefits for patients while the treatment effect wanes. Clinical experts familiar with setmelanotide agree that there is no waning in the effect of setmelanotide on hyperphagia, which is caused by defects in the MC4R pathway. Setmelanotide is an MC4R agonist that has the potential to restore lost signalling activity in the MC4R pathway by compensating for defects upstream of the receptor and directly activating MC4R neurons in the hypothalamus. Setmelanotide has potential to act as a replacement therapy to re-establish a healthy appetite and energy expenditure and thus aid body weight regulation. The effect is an on/off response. The EAG consider in their base case a discontinuation rate of 2%. However, we do not agree with this assumption as: • 1% discontinuation rate was accepted in NICE HST21 for setmelanotide in patients with obesity caused by LEPR / POMC deficiency. This was an assumption made by the EAG (PenTAG) for HST21 and was considered reasonable by their clinical advisors and chosen to represent discontinuation “due to the burden of constant injections and/or adverse events (in particular skin pigmentation which may result from setmelanotide use). • Discontinuation due to lack of efficacy or adverse events would occur soon after treatment initiation (as acknowledged by the EAG) and thus should not be considered as contributor to yearly discontinuation

Key issue #9: Evidence sources for health-state utilities. Source of utilities from mapped PedsQL scores of an external overweight/obese child population, on which hyperphagia multipliers derived from vignette studies apply. The CS has reported clinically meaningful changes in PedsQL scores for the BBS population at baseline and after 1 year of treatment with setmelanotide, which can be mapped on EQ-5D utilities directly.	Yes	There are several reasons why we consider that using PedsQL data to obtain post-treatment utilities is not appropriate: • The EAG agrees that EQ-5D is not sufficiently sensitive to pick up the effects on hyperphagia on the BBS population. • The EAG also agreed during the technical engagement meeting that existing HRQoL questionnaires, incl. PedsQL, are blunt tools to measure the quality of life of patients who have always lived with a condition (e.g., hyperphagia in BBS) or have adapted to living with that condition and do not know what it is like to live without that condition (e.g. hyperphagia). • PedsQL does not include domains that would sufficiently capture the impact of hyperphagia and hence mapping PedsQL to EQ-5D would not improve the uncertainty of the hyperphagia utility. Although one could argue that the domain entitled "How I Get Along with Others" may have some connection to hyperphagia, responses to any question of the questionnaire likely more directly reflect obesity-related HRQoL impacts rather than hyperphagia-specific effects. Like the EQ-5D, there are no questions that adequately address the impacts of hyperphagia on HRQoL. • The number of patients for whom PedsQL data are available at week 52 is very low (3 patients without cognitive impairment). Nevertheless, the EAG would like to see the HRQoL data collected during the studies and we provide this (Appendix D and Appendix F). We also conducted a scenario analysis in which PedsQL data from study RM-493-023 collected at baseline is mapped onto EQ-5D to provide the utility associated with BBS (excluding hyperphagia). This scenario analysis negates the need for a non-obesity-related BBS utility multiplier and likely captures the baseline HRQoL of the paediatric patient population more accurately than the EQ-5D as it is specific to paediatric patients. As the 023 paediatric patient cohort did not consist of patients with BMI-Z scores 0.0-1.0 or 2.5-3.0, we could not directly utilize these data to inform the baseline utilities for BBS patients by BMI-Z score. Further, the population size limited the validity of the QoL estimates, as several of the BMI-Z

		categories only consisted of a single patient and resulted in uncertain utility estimates. Therefore, we utilized the data mapped from PedsQL to EQ-5D from Riazi et al.'s "healthy population" to inform the utility for BMI-Z category 0.0-1.0, as done in the model base case. As the 023 trial data consisted of 4 patients with BMI-Z ≥4.0, we were able to utilize their PedsQL data to calculate a utility value for this subgroup. Khan et al.'s mapping algorithm (OLS 6) was used to convert these PedsQL data to EQ-5D values. The utility estimates for the remaining BMI-Z categories were linearly extrapolated from the BMI-Z 0.0-1.0 and ≥4.0 categories. The resulting ICER for this scenario is £169,018, [redacted] (note: also adjusting for the change in adult caregivers as described in Key Issue #11)
Key issue #10: Utility multiplier for Bardet-Biedl syndrome patients due to non-obesity-related comorbidities.	Yes	We agree with the EAG that the data from study RM-493-023 could be leveraged to estimate a utility multiplier for BBS due to non-obesity-related comorbidities. To explore the effect of this adjustment, we have added a scenario analysis which utilizes the baseline PedsQL data from the paediatric RM-493-023 population. These data were mapped to EQ-5D values using Khan et al.'s mapping algorithm (OLS 6). As described in the response to Key Issue #9, the baseline HRQoL data were limited for each BMI-Z category. We therefore utilized the BMI-Z category with the most patients (BMI-Z ≥ 4.0; n=4) to estimate the required utility multiplier. We compared the EQ-5D value for the BMI-Z ≥4.0 population to the BMI-Z ≥4.0 utility estimate utilized in the base-case and calculated a percent difference between the two HRQoL scores. The utility score for the RM-493-023 population was [redacted], while the value from the base case derived from Riazi et al. was 0.82. This represents a [redacted] difference, equating to a utility multiplier for non-obesity and non-hyperphagia related BBS symptoms of [redacted]. Using this multiplier instead

		of the base case BBS multiplier of 0.80, the ICER is £172,026 [redacted] (note: also adjusting for the change in adult caregivers as described in Key Issue #11) Please note that as the scenario analysis conducted in response to Key Issue #9 negates the need for a BBS utility multiplier, the approach in the current scenario analysis should not be combined with that of Key Issue #9. *Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales.* *Riazi, Afsane et al. "Health-related quality of life in a clinical sample of obese children and adolescents." Health and quality of life outcomes vol. 8 134. 15 Nov. 2010, doi:10.1186/1477-7525-8-134*
Key issue #11: Average number of carers for adult Bardet-Biedl syndrome patients	Yes	In interviews with clinical experts, we were informed that the majority of patients have caregivers including adult patients, often because of their cognitive impairment, and that they are greatly impacted by the burden of dealing with the patients' hyperphagia, including depression, anxiety and marriage break up. BBSUK are currently in the process of obtaining data on the number of caregivers for adult patients and have shared preliminary data for 121 patients, which shows that on average adult BBS patients have [redacted] caregivers which is aligns with the scenario of 0.8 caregivers run by the EAG. The number of caregivers for adults has therefore been adjusted in the economic model base case to reflect the latest BBSUK data. The ICER then becomes £198,271 for the base case (paediatric initiation) and £231,914 for the adult initiation population scenario analysis. The disutility due to a patient's hyperphagia goes beyond that of the caregiver as dealing with hyperphagia affects the whole household.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Discrepancies highlighted in the reporting of HRQoL data between company submission and Forsythe paper	EAR section 3.2.6, page 52, table 11	No	We acknowledge that there was a mistake in the reporting of the data for IWQOL-Lite (patients ≥18 years without cognitive impairment) and PedsQL (patients <18 without cognitive impairment) in the CS, where instead of reporting the data for patient without cognitive impairment the data for all patients were accidentally reported. The correct values are those reported in the Forsythe 2023 paper, i.e.:
			• IWQOL-Lite (patients ≥18 years without cognitive impairment)
			  ○ Baseline score = 70.7
			  ○ Mean improvement = +17.6 points (N = 7) – note that table 11 in EAR states this as being +12, which is incorrect
			• PedsQL (patients <18 without cognitive impairment)
			  ○ Baseline score = 83.3
			  ○ Mean improvement = +3.3 points (N = 3)
			We agree with the EAG that these discrepancies introduce confusion to the interpretation of the HRQoL results, and that however they do not impact the cost-effectiveness results as trial based HRQoL assessment do not feed into the current economic model.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Key issue #11: Average number of carers for adult Bardet-Biedl syndrome patients	On average adult BBS patients have [redacted] caregivers	On average adult BBS patients have [redacted] caregivers	The ICER then becomes £198,271 for the base case (paediatric initiation) and £231,914 for the adult initiation population scenario analysis.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: QALYs: [redacted] Undiscounted QALYs: [redacted]	Incremental costs: [redacted]	Please provide company revised base-case ICER £198,271

Sensitivity analyses around revised base case
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EAG Response to Technical engagement response form

Confidential information is highlighted as [redacted], [redacted].

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	New Info?	Response	EAG Response
Key issue #1: In the absence of a validated measure of hyperphagia, how will Bardet-Biedl syndrome patients with severe hyperphagia be identified in clinical practice?	No	The submission covers BBS patients with severe hyperphagia, as consultation with BBS experts identified that these patients will be those who would most benefit from therapy with setmelanotide. These patients experience an overwhelming, heightened, and relentless hunger that mimics feelings of starvation and results in excessive food consumption and a preoccupation with food that interferes with a patient's ability to function in daily life. The result of severe hyperphagia is early onset severe obesity, often occurring by the age of 5 years. BBS patients are treated at specialist BBS centres by clinicians experienced in the diagnosis and management of BBS, and who use their expert judgement to identify and assess hyperphagia. BBS experts can and will identify severe hyperphagia through careful questioning of the patient and / or caregiver and based on the patient history. Indicators clinicians will look for include: ▸ Patient reporting that they are continuously hungry, even despite recent food intake	The CS focuses on BBS patients with severe hyperphagia. However, as noted by the company here, and in response to clarification question A1, there is no validated measure of the severity of hyperphagia symptoms for BBS patients. As such, participants in the company trials were retrospectively assumed to have had severe hyperphagia only if they had responded to setmelanotide. In clinical practice, hyperphagia severity will be assessed prospectively, in advance of treatment initiation. In clarification response A1, the company noted the challenges of prospective assessment of hyperphagia, particularly in relation to the assessment of hunger and overeating symptoms. In the absence of a robust measure of hyperphagia severity, the prospective assessment of symptoms introduces uncertainty in terms of

		▸ Patient overeating at meals and eating constantly, including several times during the night ▸ Caregivers having difficulty managing the patient's eating habits and having to hide / ration food ▸ Patient experiencing distress or inappropriate behavioural response if denied food ▸ Patient having rapid or continued weight gain despite diet and exercise regimen In the vignette study conducted by Rhythm Pharmaceuticals, severe hyperphagia was described in terms of subjective experience, observable behaviours and its impact as described below, reflecting the indicators clinicians will look for in their assessment of hyperphagia severity: **Subjective Experience** • You **almost never feel full** after a **normally sized meal** • You become **hungry again almost immediately** after eating a meal • Thinking about food **almost always interferes** with your **normal activities** of daily living **Observable Behaviors** • You overeat to the point of **discomfort at most meals** • You eat **almost constantly** • You eat during the **hour** before you go to bed **almost every night**	the number of patients correctly identified as having severe hyperphagia in clinical practice. The EAG consider that the potential impact on the ICER of patients with moderate hyperphagia symptoms also being treated with setmelanotide should be explored in a scenario analysis. The EAG report (Section 6.2) considers the scenario where a proportion (40%) of patients treated with setmelanotide begin the model with moderate hyperphagia, and the rest (60%) with severe hyperphagia. These proportions were based on the company's response to the EAG's clarification questions. The probabilistic ICER for the paediatric population increases from £194,072 in the company's updated base-case to £230,084 when a proportion of patients have moderate hyperphagia.

		• You **eat** a large number of calories when you wake up **during the night almost every night** • You try to **sneak food** without people knowing **almost every day** **Impact** • You become **extremely distressed or upset** when **denied food** • Because of hunger and eating behavior, you have **severe problems performing daily activities** such as self-care, getting around, leisure activities and work or school • Because of hunger and eating behavior, you have **severe problems with your relationships** with family and friends In the RM-493-023 and RM-493-022 clinical studies hyperphagia was not measured because no tool exists for measuring hyperphagia that is specific for BBS patients. The Dyken's hyperphagia questionnaire developed for Prader-Willi syndrome (PWS) was not considered appropriate for the studies because it is a caregiver-reported instrument since patients with PWS are unable to reliably self-report (Fehnel et al. 2015) and thus would not capture the personal and subjective nature of hyperphagia which is critical in BBS. While patients with BBS have severe hyperphagic behaviours, these behaviours don't completely align with those found in PWS (and therefore measured by Dyken's).	

		Fehnel et al. 2015. Development of the Hyperphagia Questionnaire for Use in Prader-Willi Syndrome Clinical Trials. Presented at: ISPOR 20th Annual International Meeting	
Key issue #2: Are the findings of studies RM-493-023 and RM-493-022 generalisable to NHS practice?	No	The studies were conducted in the US, Canada, the UK, France, and Spain, most patients being from the US. In terms of ethnicity, in study RM-493-023 77.3% of patients where white, and in study RM-493-022, 86.7% of patients were white. The Office of National Statistics states that in 2021 in England and Wales, 81.7% of the population identified as white. It is therefore reasonable to assume that the data from the setmelanotide trials can be considered generalisable to the UK decision making context. We note in the attached engagement papers that the British Obesity and Metabolic Surgery Society (BOMSS) submission states in their response to question 18, that the clinical trials on setmelanotide reflect current UK clinical practice. We acknowledge the EAG's suggestion of using the CRIBBS registry to characterise the UK based BBS patient population and have taken this into consideration. However, the number of UK patients [redacted] in the CRIBBS registry is not enough to characterise the UK BBS population. Furthermore, only a subset of CRIBBS patients have reliable longitudinal data on weight gain and the sample used for definition of the null hypothesis, following recommendation of regulatory authorities, does not detail the country of origin of patients.	In terms of generalisability to NHS practice, the EAG consider the relevant comparison of interest to be between the BBS patients included in the company trials and the BBS patients in the UK, not the UK general population. Although the CRIBBS database has a small number of UK patients, it is still greater than the [redacted] UK patients included in the company trials (CS Table 9). Given the absence of any other data source the CRIBBS data would still provide valuable information to assess the generalisability of study findings in terms of patient characteristics.
Key issue #3: How reliable and valid are the clinical	Yes	A response to clarification question A17 was provided. The clinical study report was shared with the EAG in response to the EAG report factual accuracy check and includes	We thank the company for providing the baseline characteristics and additional information on the number and proportion of

effectiveness results for key outcomes reported by RM-493-023?		information on the multiple imputation approach used for the different outcome, including the number of patients for whom data was imputed for different outcome. The baseline characteristics for participants whose follow-up data at 52 weeks was imputed and for participants whose follow up data was not imputed, requested in clarification question A16 are provided with our response (Appendix A). We also now provide additional information on the number and proportion of patients for whom data was imputed for key endpoints at week 52 (Appendix B).	patients with imputed data. We note that the CSR was only available to the EAG with the company's factual accuracy check (FAC) and that the company's FAC response to clarification A17 does not reference the CSR. The FAC response states: "*Response to A17 was provided and is included below*: *"There are no missing data in the 14 weeks outcome in the RM-493-023 trial, regardless of the treatment arm. Only one patient discontinued therapy during the placebo-controlled period and that patient was randomised to placebo. The reason for discontinuation was adverse event (anaphylaxis) occurring while on placebo. Thus, there is no answer to the question on the imputation model."* The CSR does provide some information on imputation methods and the numbers of patients with imputed data per outcome are reported in the footnotes of results tables. However, the EAG note that the CSR includes both patients with BBS and Alstrom Syndrome. Therefore, using the CSR as the sole basis to inform the EAG assessment of the impact of missing data here would be inadvisable. The additional information provided in Appendix B provides the numbers of patients

			with an imputed value for 11 key outcomes. Imputation was carried out for five of these 11 outcomes at 52 weeks follow-up. Approximately [redacted] of patients had data imputed at week 52 for each of these five outcomes. The EAG deduce that results reported in the CS for these outcomes are not based on a multiple imputation approach. Information gleaned from the footnotes of the CSR tables indicates that reasons for missing data for these five outcomes were due to [redacted]. As such, these values were imputed using the patient's baseline' value, constituting a treatment failure approach. It is not clear whether this is study baseline, at point of randomisation, or active treatment baseline, at the point patients received setmelanotide. [redacted] of missing or imputed outcome data is considered substantial missingness. However, the imputation method used would likely bias the estimate towards the null. As such, the EAG have revised the risk of bias assessment rating for the missing data domain from 'serious' to 'moderate' risk of bias, for six of the eight outcomes included in EAG report Table 10 (Risk of Bias assessment). An amended table 10 is included in the addendum. Please see key

			issue #5 for the EAG assessment of the implications of the amended risk of bias assessments for the economic model. The information provided in the CSR and Appendix B did not allow the EAG to directly assess the number of patients who had data imputed due to having less than ~52 weeks of setmelanotide treatment at the time of primary analysis (i.e. missingness due to study design). The baseline characteristics provided in Appendix A are for the full analysis set (n=43), split by participants initially enrolled in either the setmelanotide group or placebo group. The EAG consider characteristics to be balanced across the placebo and setmelanotide arms, for participants with imputed and non-imputed values. However, we note some imbalances within arm. For example, for participants <12 years old the average age of those with imputed values was [redacted] and [redacted] years and those with observed values were [redacted] and [redacted] years old in the setmelanotide and placebo arms respectively. The EAG note the reporting inconsistencies within the CS and across publications

			associated with the CS. See section 3.2.5.1 of the EAG report for details.
Key issue #4: What is the impact of potential bias arising from absence of randomised, controlled comparisons for key clinical outcomes at 52 weeks follow-up in RM-493-023?	No	BBS is a rare disease making traditional comparative clinical studies a great challenge. Strong phase II data which showed that 70% of patients achieved a ≥5% weight loss at 3 months, informed the study design. The design of the Phase III was chosen based on discussions with regulatory authorities and clinical study investigators to optimise patient retention in the study, maximise patient exposure to active therapy and minimise the risk of unblinding due to the impact on hyperphagia and to hyperpigmentation. Advice from clinical study investigators indicated that patients would be reluctant to continue daily subcutaneous injections for 52 weeks without experiencing any clinical effect. We also acknowledge a small, negligible initial placebo effect, but we believe that this effect remains constant until week 52, and thus we do not believe this placebo effect shows an apparent regression to the mean. Hunger scores, BMI, BMI-Z and weight remained virtually unchanged for patients on placebo during the initial 14-week treatment phase, and hence would not require adjusting for. This is supported by studies with semaglutide (STEP 1, STEP 5 and STEP TEENS) which also show that the placebo response plateaus around week 16. Though note that the semaglutide studies include active lifestyle intervention in both arms, which may contribute to a larger effect in the placebo arm.	The EAG agree with the company that it is challenging to run phase-III studies in populations with a rare condition. However, these challenges do not negate the potential for bias in the 52-week data, which is equivalent to an uncontrolled, before-after study. The absence of a control-group means it is not possible to conclude that the observed treatment effect is entirely attributable to setmelanotide. The EAG do not agree that the observed placebo effect is small or negligible. As the company note the figures presented in response to clarification question A15 and figure 6 of the CS show that the patients initially randomised to placebo show a drop which is maintained for 14 weeks, and then when they switch to setmelanotide their hunger score / weight / BMI / BMI-Z drops further to the level of those originally randomised to setmelanotide. This highlights that the larger drop seen for those initially randomised to setmelanotide is a combination of the placebo (or regression to the mean) effect plus the treatment effect. The difference between the level for the placebo group from week 14 and week 24 provides a treatment effect that adjusts for

		By comparison hunger scores, BMI, BMI-Z and weight are significantly reduced during the first 14 weeks of setmelanotide treatment. The figures presented in response to clarification question A15 and figure 6 of the CS show that from 14 weeks all patients are on setmelanotide, and that patients initially randomised to placebo then start experiencing a reduction in hunger scores weight / BMI / BMI-z with the curves of the two arms merging around week 24.	placebo / regression to the mean. This is still a substantial treatment effect, but not as big as that seen in those originally randomised to setmelanotide.
Key issue #5: To what extent does the selective outcome reporting of exploratory outcomes reduce confidence in clinical effectiveness and cost-effectiveness results?	Yes	All relevant outcomes were reported. Study reports have since been shared as response to the EAG report factual accuracy check as requested by the EAG. Table 7 of the RM-493-023 study report (file 2.4.1.2.25 rm-493-023-body) lists all the protocol amendments, incl. dates and substantive changes. The last amendment was implemented on 9th September 2020, which was before the first data readouts. The first efficacy analyses for the CSR and for publication were carried out on 24th of May 2021, i.e. after the last protocol amendment was implemented. Prior to that a safety analysis was carried out in October 2019, but this was limited to safety outcomes. We also now share the updated study protocol for study RM-493-023 (Appendix C) as requested as well as PedsQL and IWQOL data for this study (Appendix D and F). Nevertheless, HRQoL data collected in study RM-493-023 are not appropriate to determine QALYs for the following reasons:	We thank the company for providing the information that was not available to the EAG in the original submission, including the full study protocol and the clinical study reports (CSR) for RM-493-023, along with the details of the protocol amendments and the dates at which they occurred with respect to the start of the first efficacy analyses. We were able to ascertain that the efficacy outcomes included in the EAG report were pre-specified in the provided study protocol for RM-493-023, although most were pre-specified using 12-year-old age cut-off for the participants age subgroups. For the CS, the majority of outcomes were reported using 18 years as the cut-off (with the exception of the primary outcome, which used the ≥12 years cut-off). We have assumed that the age subgroup analyses using the 18-year-cut-off were post-hoc analyses produced specifically for

		• EQ-5D is not sufficiently sensitive to pick up effects on hyperphagia. The company submission included the rationale for this (that hyperphagia is not a domain that is covered by EQ-5D and therefore it will miss the impacts of treatment on hyperphagia.) This is similar to other disease areas/conditions where EQ-5D is known to be insensitive, such as insomnia, fatigue, blindness, and deafness. For this reason, utility estimates were estimated through using a vignette study and the EAG accepted this rationale.
		• Notwithstanding this, the PedsQL dataset was too small to allow mapping onto EQ-5D and VAS scores and did not allow separate analysis at 14 and 52 weeks.
		  ○ Few patient data available at week 52 (3 patients without cognitive impairment, 6 with cognitive impairment)
		  ○ Effect of setmelanotide at 14 weeks would have been too small to be captured by the tools
		• As noted by the EAG in their report, there are no known mapping algorithms for IWQOL scores
		• Furthermore, IWQOL and PedsQL do not include domains that would sufficiently capture the impact of hyperphagia and hence mapping these to EQ-5D would not improve the uncertainty of the hyperphagia utility and thus would not improve uncertainty of the ICER.
			the submission to NICE, to match the scope, although this was not explicitly stated.
			
			Given this new information, and the additional information provided regarding imputation, the EAG has revised the overall risk of bias ratings for six of the eight outcomes considered in Table 10 of the EAG report. The revised assessment has been upgraded from 'serious' to 'moderate' risk of bias. We note that this revised rating of 'moderate risk of bias' applies to two of the four outcomes that inform the economic model. We have revised the rating for the outcomes 'proportions of patients aged <18 years achieving at least 0.2 and 0.3 point reduction in BMI Z-score' from 'serious' to 'moderate' risk of bias. However, the assessment of the BMI and BMIz score shift outcomes has not been revised and is still classed as being at serious risk of bias. An amended Table 10 is included in the addendum.

		• SF-36 and SF-10 like IWQOL and PedsQL do not include domains that would sufficiently capture the impact of hyperphagia and hence mapping these to EQ-5D would not improve the uncertainty of the ICER. Also, the EAG acknowledge in their report that using SF-36 would result in additional complexity to the model and did not pursue this change in the model.	
Key issue #6: All responders are assumed to move to the mild hyperphagia state, independent of change in BMI-Z / BMI.	Yes	The EAG used in their base case an alternative scenario where responders can move either to moderate or mild hyperphagia state with the proportions in each state based on the proportion of responders who have a [redacted] or [redacted] class reduction in BMI-Z. This is based on the assumption that patients who experienced BMI-Z reduction of [redacted] class had moved to moderate hyperphagia and that patients who experienced [redacted] class reduction moved to mild hyperphagia. While we understand the rationale, we do not agree with it, for the following reasons: • To be considered a responder to setmelanotide treatment, patients need to attain significant sustained change in BMI-Z over one year. To achieve this, patients need to experience a substantial change in eating habits which can only be brought about by experiencing mild hyperphagia, as moderate hyperphagia would not yield the observed reduction in BMI-Z. See below definition of moderate and mild hyperphagia. Thus, a [redacted] class reduction in BMI-z does not indicate a move to moderate hyperphagia instead of mild	The company argue that the impact on BMI-Z is not a reliable proxy for impact on hyperphagia, however hyperphagia was not measured in their studies and we are left having to infer it from BMI-Z. This is also what the company use to justify their assumption that all patients will move to mild hyperphagia. We still consider it unlikely that all patients will move from severe hyperphagia to mild hyperphagia, and expect that instead there will be a spread of effects with some patients having a bigger response than others. The variability in change in BMI-Z supports this. The company give their definition of moderate hyperphagia and argue that patients in this state would not be able to achieve the weight loss observed in their study. We would agree with that, but also

		hyperphagia; it indicates a slower change in eating habits. • The impact on BMI-Z is not a reliable proxy for impact on hyperphagia, as the benefits from hyperphagia reduction go beyond those reflected by weight loss and include impact on quality of life due to the reduction in hunger, improvement in eating habits and disruption of sleep, mood and emotions, leisure activities, and relationships with friends and family. • Clinical experts in BBS agree that when treated with setmelanotide obese BBS patients' with severe hyperphagia at baseline change from severe to mild, independently of the magnitude of weight lost. • The [redacted] class reduction in BMI-Z is an underestimation of the effect on BMI-Z on these patients because of the limitations of the lower and upper BMI-Z score class ranges which are less sensitive to changes in BMI-Z. ○ The BMI-Z score classes defined in the study were <1, 1 to <2, 2 to <2.5, 2.5 to <3, 3 to < 3.5, 3.5 to <4, >4, i.e., at the extremities the range in BMI-Z is greater than the 0.5 ranges in the middle classes. ○ There were [redacted] patients with baseline BMI-Z >4 (some much greater than 4) and [redacted] with baseline BMI-Z [redacted]. If classes at the extremities had a range of 0.5 (as the classes between 2 and 4), then	believe that patients in the moderate health state as described also would not have a utility multiplier of 0.72 (assumed for moderate hyperphagia), and instead a lower multiplier, closer to that for severe. It is more useful to consider the EAG assumption in terms of the utility multiplier. The EAG are assuming that not everyone will move from a utility multiplier of [redacted] all the way to a utility multiplier of 0.91. Instead, a proportion will have a large but more modest improvement to 0.72. Because the company did not measure hyperphagia in their study, the proportion that move to a utility multiplier of 0.91 is uncertain. In the absence of other information we used the change in BMI-Z to estimate the proportion who would have a utility multiplier of 0.91, with the rest achieving a utility multiplier of 0.72. The company make a fair point about their uneven class definitions. Using the more finely defined classes in Appendix E of the company's Technical Engagement response, we estimate that in responders [redacted] experience [redacted] change in class, and [redacted] experience a [redacted] or more change. If we

		for patients with BMI-Z >4, [redacted] would have experienced a [redacted] reduction in BMI-Z, [redacted] patients would have experienced a [redacted] reduction in BMI-Z and [redacted] would have experienced a [redacted] reduction. The [redacted] with baseline BMI-Z [redacted] points in BMI-Z and was no longer obese, which would correspond to a [redacted] reduction. Based on classes being defined by increments in 0.5 BMI-Z scores, the mean shift in classes is [redacted], which is closer to [redacted] than [redacted]. ○ Furthermore, the mean difference in BMI-Z score from baseline is [redacted], which corresponds to [redacted] class change ([redacted]/0.5), again nearer to a [redacted]-class shift than a [redacted]-class shift. Please refer to new evidence document Appendix E. Thus, we maintain that a [redacted]-class change better reflects the impact on BMI-Z experienced by patients. ○ The choice of the class ranges was based on availability of published data to estimate the risk of comorbidities and the disutility of obesity. • The assumptions for hyperphagia transitions used in our base case are conservative, as we have not assumed any transitions occurred to no hyperphagia state.	assume that those with [redacted] change have no change in hyperphagia, and those with [redacted] or more change in class have mild hyperphagia, then the average utility multiplier is [redacted] (=[redacted]). This is very similar to the average utility multiplier from the EAG basecase of [redacted] ([redacted]), and so would give very similar results. Note the above assumes that the estimates of change in BMI-Z from study RM-493-023 are robust. However, these do not adjust for the placebo effect, and there was missing outcome data that may be informative. We therefore consider our original base-case to be a reasonable estimate of the impact of hyperphagia on utility, albeit noting the considerable uncertainty in this.

		MODERATE HYPERPHAGIA **Subjective Experience** • You **usually do not feel full** after a **normally sized meal** • You become **hungry again within 1 hour** after eating a meal • Thinking about food **often interferes** with your **normal activities** of daily living **Observable Behaviors** • You **often** overeat to the point of **discomfort** • You eat **more than 3 meals** per day with **more than 3 snacks** • You **often** eat during the **hour** before you go to bed • You **eat** a large number of calories when you wake up **during the night about 2-3 times per week** • You try to **sneak food** without people knowing about **twice per week** **Impact** • You become **moderately distressed or upset** when **denied food** • Because of hunger and eating behaviour, you have **moderate problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behaviour, you have **moderate problems with your relationships** with family and friends **MILD HYPERPHAGIA**	

		Subjective Experience • You **sometimes do not feel full** after a **normally sized meal** • You become **hungry again within 2 hours** after eating a meal • Thinking about food **sometimes interferes** with your **normal activities** of daily living **Observable Behaviors** • You **sometimes** overeat to the point of **discomfort** • You eat **3 meals** per day with **more than 2 snacks** • You **sometimes** eat during the **hour** before you go to bed • You **eat** when you wake up **during the night about once per week** • You **occasionally** try to **sneak food** without people knowing **Impact** • You become **mildly distressed or upset** when **denied food** • Because of hunger and eating behaviour, you have **slight problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behaviour, you have **slight problems with your relationships** with family and friends Regarding the request for further data to enable mapping between hunger score and hyperphagia state, no further data is available. Also, because there is a multifactorial	

		correlation between hunger and hyperphagia, using extent of hunger in isolation is not an effective means of measuring hyperphagia.	
Key issue #7: Size of the treatment effect on BMI-Z in responders to setmelanotide in the paediatric population uncertain	Yes	The EAG noted that there is variability in movement between BMI-Z classes in patients in study RM-493-023 and felt this was consistent with a [redacted]-class reduction in BMI-Z instead of our assumed [redacted]-class reduction. The EAG suggested that we use a standard distribution to estimate the treatment effect instead of using the current approach. Indeed, if we take the baseline mean and assume a normal distribution with standard deviation equal to the baseline SD, then we can calculate the expected proportion of patients falling into each BMI-Z category after treatment response. However, this would require altering the structure of the model which we do not believe is necessary as the current approach is not unreasonable. As explained for key issue #6, the [redacted] class reduction in BMI-Z is an underestimation of the effect on BMI-Z on these patients because of the limitations of the lower and upper BMI-Z score class ranges which are less sensitive to changes in BMI-Z. • The BMI-Z score classes defined in the study were <1, 1 to <2, 2 to <2.5, 2.5 to <3, 3 to < 3.5, 3.5 to <4, >4, i.e., at the extremities the range in BMI-Z is greater than the 0.5 ranges in the middle classes. • There were [redacted] patients with baseline BMI-Z >4 (some much greater than 4) and [redacted] with baseline BMI-Z [redacted]. If classes at the extremities had a range of 0.5 (as the classes between 2 and 4), then for patients with BMI-Z >4, [redacted] would have	We appreciate that the class categories are uneven, and this may impact the numbers of classes shifted at the extremities. Using the new classifications provided by the company in Appendix E of their Technical Engagement response, they obtain a mean class reduction of [redacted]. We believe this is likely an over-estimate due to not accounting for the "placebo effect", and note this outcome is rated at serious risk of bias (see response to Issue #5). However, we acknowledge that the mean class reduction is likely to be somewhere between a [redacted]- or [redacted]-class reduction. The model doesn't allow a distribution of BMI-Z reductions however, and so we can only look at the results with a [redacted]-class or [redacted]-class reduction and assume the truth may lie somewhere between the two. It is not clear how the results from the trial would compare with clinical practice. Whilst clinical practice will involve active management of diet and exercise that were not allowed in the trial, these interventions are not considered effective for BBS patients, and there is no evidence to show whether they would be effective for BBS

		experienced a [redacted] reduction in BMI-Z, [redacted] patients would have experienced a [redacted] reduction in BMI-Z and [redacted] would have experienced a [redacted] reduction. The [redacted] with baseline BMI-Z [redacted] points in BMI-Z and was no longer obese, which would correspond to a [redacted] reduction. Based on classes being defined by increments in 0.5 BMI-Z scores, the mean shift in classes is [redacted], which is closer to [redacted] than [redacted]. • Furthermore, the mean difference in BMI-Z score from baseline is [redacted], which corresponds to [redacted] class change ([redacted]/0.5), again nearer to a [redacted]-class shift than a [redacted]-class shift. Please refer to Appendix E. Thus, we maintain that a [redacted]-class change better reflects the impact on BMI-Z experienced by patients. • The choice of the class ranges was based on availability of published data to estimate the risk of comorbidities and the disutility of obesity. We believe that the paediatric data show consistency of reduction in BMI-Z and consistency in clinical benefits for the patients and that using a reduction of [redacted] classes on average is a fair representation of change in that population and a valid hypothesis for the model. Furthermore, in clinical practice which will involve multidisciplinary care including the management of obesity (incl. active management of diet and exercise), the effect of hyperphagia reduction on BMI-Z in patients treated with setmelanotide is anticipated to be greater than that observed in the clinical trial, in which changes to diet and exercise were not allowed.	patients taking setmelanotide. The lack of a control in the trial beyond 14 weeks also adds to the uncertainty as to the applicability of the trial results in clinical practise.

Key issue #8: BMI-Z / BMI reduction is extrapolated into the long-term	No	While the EAG do acknowledge in their report that the evidence for GLP-1 receptor agonists show only a small waning of treatment effect at 104 weeks compared with 52, suggesting that interventions that act on hunger have the potential to achieve sustained effects in the short to medium term, in their base case the EAG assume 1% patients per year return to their original BMI/ BMI-Z. We do not agree with this assumption, as in patients who respond to setmelanotide the hyperphagia benefit is retained, with the consequent change in eating habits and thus patients experience a benefit in BMI/BMI-Z which they would not experience if they were not on setmelanotide. Patients with severe hyperphagia who are untreated are on an ever increasing weight trajectory, hence when treated with setmelanotide even if an increase in BMI/BMI-Z can be observed in the long term, the benefit is retained compared to the BMI/BMI-z the patient would have achieved if left untreated. Note that in our base case the model is conservative, as: • It does not account for increase in BMI/ BMI-Z in patients with severe hyperphagia not treated with setmelanotide. • Patients who stop setmelanotide treatment revert back to their baseline BMI/BMI-Z score category immediately, with no tapering of treatment effect, i.e., without accounting for the benefits for patients while the treatment effect wanes. Clinical experts familiar with setmelanotide agree that there is no waning in the effect of setmelanotide on	We agree with the company that treatment efficacy is modelled in a simplistic way, assuming no change in BMI/BMIz category over time for given response state. This makes it difficult to model waning of treatment effect over time, and so the inclusion of a discontinuation rate is a crude way to achieve that. The 1% discontinuation rate used in HST21 for setmelanotide in patients with obesity caused by LEPR / POMC deficiency was based on assumption and clinical opinion, and represents discontinuation due to adverse events and issues with injections. However, there is data available from Study RM-493-023 on discontinuations which are consistent with a 2% discontinuation rate due to lack of efficacy. We prefer to use an assumption based on data from RM-493-023. Note that the 2% discontinuation rate reduces the ICER compared with a 1% discontinuation rate, due to lower lifetime treatment costs which outweigh the reduced HRQoL benefits.

		hyperphagia, which is caused by defects in the MC4R pathway. Setmelanotide is an MC4R agonist that has the potential to restore lost signalling activity in the MC4R pathway by compensating for defects upstream of the receptor and directly activating MC4R neurons in the hypothalamus. Setmelanotide has potential to act as a replacement therapy to re-establish a healthy appetite and energy expenditure and thus aid body weight regulation. The effect is an on/off response. The EAG consider in their base case a discontinuation rate of 2%. However, we do not agree with this assumption as: • 1% discontinuation rate was accepted in NICE HST21 for setmelanotide in patients with obesity caused by LEPR / POMC deficiency. This was an assumption made by the EAG (PenTAG) for HST21 and was considered reasonable by their clinical advisors and chosen to represent discontinuation "due to the burden of constant injections and/or adverse events (in particular skin pigmentation which may result from setmelanotide use). • Discontinuation due to lack of efficacy or adverse events would occur soon after treatment initiation (as acknowledged by the EAG) and thus should not be considered as contributor to yearly discontinuation	

Key issue #9: Evidence sources for health-state utilities. Source of utilities from mapped PedsQL scores of an external overweight/obese child population, on which hyperphagia multipliers derived from vignette studies apply. The CS has reported clinically meaningful changes in PedsQL scores for the BBS population at baseline and after 1 year of treatment with setmelanotide, which can be mapped on EQ-5D utilities directly.	Yes	There are several reasons why we consider that using PedsQL data to obtain post-treatment utilities is not appropriate: • The EAG agrees that EQ-5D is not sufficiently sensitive to pick up the effects on hyperphagia on the BBS population. • The EAG also agreed during the technical engagement meeting that existing HRQoL questionnaires, incl. PedsQL, are blunt tools to measure the quality of life of patients who have always lived with a condition (e.g., hyperphagia in BBS) or have adapted to living with that condition and do not know what it is like to live without that condition (e.g. hyperphagia). • PedsQL does not include domains that would sufficiently capture the impact of hyperphagia and hence mapping PedsQL to EQ-5D would not improve the uncertainty of the hyperphagia utility. Although one could argue that the domain entitled "How I Get Along with Others" may have some connection to hyperphagia, responses to any question of the questionnaire likely more directly reflect obesity-related HRQoL impacts rather than hyperphagia-specific effects. Like the EQ-5D, there are no questions that adequately address the impacts of hyperphagia on HRQoL. • The number of patients for whom PedsQL data are available at week 52 is very low (3 patients without cognitive impairment).	We thank the company for providing this additional analysis. The EAG has three major concerns: 1. The Khan (2014) algorithm applied to map PedsQL scores to utility scores was designed to be applied to individual patient scores. The company performs the mapping on the average, rather than mapping for each individual patient and then perform the average. Because utilities are not linear, this approach gives biased estimates of utilities. We re-analysed the data mapping PedsQL for the 4 individuals, and found the average utility for the n=4 sample is of [redacted] rather than [redacted] obtained by the company. In the Addendum to our report we provide results for the company updated base-case scenario in response to Key Issue 9 with the corrected utility value for BMI-Z>=4. 2. The EAG is also concerned that the incorrect use of Khan's mapping approach (on the means rather than individual patient scores) was also used to obtain the utility scores from the Riazi study. If this is the case, then all baseline utilities based on the Riazi study are flawed and unreliable.

		Nevertheless, the EAG would like to see the HRQoL data collected during the studies and we provide this (Appendix D and Appendix F). We also conducted a scenario analysis in which PedsQL data from study RM-493-023 collected at baseline is mapped onto EQ-5D to provide the utility associated with BBS (excluding hyperphagia). This scenario analysis negates the need for a non-obesity-related BBS utility multiplier and likely captures the baseline HRQoL of the paediatric patient population more accurately than the EQ-5D as it is specific to paediatric patients. As the 023 paediatric patient cohort did not consist of patients with BMI-Z scores 0.0-1.0 or 2.5-3.0, we could not directly utilize these data to inform the baseline utilities for BBS patients by BMI-Z score. Further, the population size limited the validity of the QoL estimates, as several of the BMI-Z categories only consisted of a single patient and resulted in uncertain utility estimates. Therefore, we utilized the data mapped from PedsQL to EQ-5D from Riazi et al.'s "healthy population" to inform the utility for BMI-Z category 0.0-1.0, as done in the model base case. As the 023 trial data consisted of 4 patients with BMI-Z ≥4.0, we were able to utilize their PedsQL data to calculate a utility value for this subgroup. Khan et al.'s mapping algorithm (OLS 6) was used to convert these PedsQL data to EQ-5D values. The utility estimates for the remaining BMI-Z categories were linearly extrapolated from the BMI-Z 0.0-1.0 and ≥4.0 categories. The resulting ICER for this scenario is £169,018, with undiscounted QALYs [redacted] (note: also adjusting for the change in adult caregivers as described in Key Issue #11)	The EAG did not have access to the data from Riazi to correct for this, but did map the single patient PedQL score in the BMI-Z 0.0 – 1.0 category from study RM-493-023 to obtain a utility estimate of [redacted] for BMI-Z 0.0 – 1.0. The EAG then used linear interpolation based on this estimate and the [redacted] estimate for BMI-Z >=4 to estimate utilities for other BMI-Z categories. The EAG use this approach in their updated base-case reported in the Addendum to the EAG report. The EAG would like to stress, however, that this approach is not ideal and there is therefore given considerable uncertainty around the baseline utilities. 3. The EAG is unclear whether the 9 patients were considered for selection into this analysis represent all patients with PedsQL measures at baseline. The Forsythe paper states that there are 9 patients without cognitive impairment who have data at both baseline and 52 weeks. However, 52 week data are not necessary to inform the baseline utilities in the model and if more patients had a baseline PedsQL measure then these should be included. The company provide baseline PedsQL data for 11 patients in Appendix D of their response

			to Technical Engagement, but again the EAG is unclear if these 11 patients are all those with baseline PedsQL data. Of the 9 patients, only 4 were included in the analysis, due to only one BMI-Z category (>=4) having more than 1 patient. The other BMI-Z categories were linearly extrapolated. The included patient scores are therefore a very select sample and may not be representative of all BBS patients at baseline. Note also there is a typo in the company's response – the figures given are for discounted QALYS (not undiscounted QALYs).
Key issue #10: Utility multiplier for Bardet-Biedl syndrome patients due to non-obesity-related comorbidities.	Yes	We agree with the EAG that the data from study RM-493-023 could be leveraged to estimate a utility multiplier for BBS due to non-obesity-related comorbidities. To explore the effect of this adjustment, we have added a scenario analysis which utilizes the baseline PedsQL data from the paediatric RM-493-023 population. These data were mapped to EQ-5D values using Khan et al.'s mapping algorithm (OLS 6). As described in the response to Key Issue #9, the baseline HRQoL data were limited for each BMI-Z category. We therefore utilized the BMI-Z category with the most patients (BMI-Z ≥ 4.0; n=4) to estimate the required utility multiplier. We compared the EQ-5D value for the BMI-Z ≥4.0 population to the BMI-Z ≥4.0 utility	We thank the company for providing this additional analysis. The same data analysis is used as in response to Key Issue #9 above, but applied to the multiplier for BBS due to non-obesity-related comorbidities, rather than directly to the utilities for each BMI-Z category. We therefore have the same concerns, as outlined above in response to Key Issue #9. Mapping individual scores and then averaging gives a utility score of [redacted], rather

		estimate utilized in the base-case and calculated a percent difference between the two HRQoL scores. The utility score for the RM-493-023 population was 0.79, while the value from the base case derived from Riazi et al. was 0.82. This represents a 2.57% difference, equating to a utility multiplier for non-obesity and non-hyperphagia related BBS symptoms of 0.9743. Using this multiplier instead of the base case BBS multiplier of 0.80, the ICER is £172,026 with undiscounted QALYs [redacted] (note: also adjusting for the change in adult caregivers as described in Key Issue #11) Please note that as the scenario analysis conducted in response to Key Issue #9 negates the need for a BBS utility multiplier, the approach in the current scenario analysis should not be combined with that of Key Issue #9. *Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales.* *Riazi, Afsane et al. "Health-related quality of life in a clinical sample of obese children and adolescents." Health and quality of life outcomes vol. 8 134. 15 Nov. 2010, doi:10.1186/1477-7525-8-134*	than [redacted]. This gives a corrected non-obesity and non-hyperphagia related BBS symptoms utility multiplier of [redacted]/0.82=[redacted]. In the Addendum to the EAG report we provide results for the company updated base-case scenario in response to Key Issue 10 using a utility multiplier of [redacted]. However, the 0.82 figure from Riazi is likely also calculated by applying the mapping to the averages (rather than averaging the individual mappings), and so the EAG have concerns about this value, and hence any multipliers derived using it. Note that the results of the companys scenario for Key Issue #9 are very similar to the results for the companys scenario for Key Issue #10. This is because the same data are used to make the adjustment, in different, but related ways. Note also there is a typo in the company's response – the figures given are for discounted QALYS (not undiscounted QALYs).
Key issue #11: Average number of carers for adult	Yes	In interviews with clinical experts, we were informed that the majority of patients have caregivers including adult patients, often because of their cognitive impairment, and that they are greatly impacted by the burden of dealing	The EAG prefer to use data on which to base this assumption, so are happy in principle with the adjustment in the

Bardet-Biedl syndrome patients		with the patients' hyperphagia, including depression, anxiety and marriage break up. BBSUK are currently in the process of obtaining data on the number of caregivers for adult patients and have shared preliminary data for 121 patients, which shows that on average adult BBS patients have [redacted] caregivers which is aligns with the scenario of 0.8 caregivers run by the EAG. The number of caregivers for adults has therefore been adjusted in the economic model base case to reflect the latest BBSUK data. The ICER then becomes £198,271 for the base case (paediatric initiation) and £231,914 for the adult initiation population scenario analysis. The disutility due to a patient's hyperphagia goes beyond that of the caregiver as dealing with hyperphagia affects the whole household.	companys model to reflect the latest BBSUK data. Note however that the EAG has not seen the BBSUK data to verify this. The EAG have updated their base-case to include [redacted] caregivers.

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	New Info?	Response	EAG Response

Additional issue 1: Discrepancies highlighted in the reporting of HRQoL data between company submission and Forsythe paper	EAR section 3.2.6, page 52, table 11	No	We acknowledge that there was a mistake in the reporting of the data for IWQOL-Lite (patients ≥18 years without cognitive impairment) and PedsQL (patients <18 without cognitive impairment) in the CS, where instead of reporting the data for patient without cognitive impairment the data for all patients were accidentally reported. The correct values are those reported in the Forsythe 2023 paper, i.e.:
			• IWQOL-Lite (patients ≥18 years without cognitive impairment)
			  ○ Baseline score = 70.7
			  ○ Mean improvement = +17.6 points (N = 7) – note that table 11 in EAR states this as being +12, which is incorrect
			• PedsQL (patients <18 without cognitive impairment)
			  ○ Baseline score = 83.3
			  ○ Mean improvement = +3.3 points (N = 3)
			We agree with the EAG that these discrepancies introduce confusion to the interpretation of the HRQoL results, and that however they do not impact the cost-effectiveness results as trial based HRQoL assessment do not feed into the current economic model.
				Thank-you for resolving this.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG Response
Key issue #11: Average number of carers for adult Bardet-Biedl syndrome patients	On average adult BBS patients have [redacted] caregivers	On average adult BBS patients have [redacted] caregivers	The ICER then becomes £198,271 for the base case (paediatric initiation) and £231,914 for the adult initiation population scenario analysis.	The EAG has updated its basecase to use a value of [redacted] caregivers per adult BBS patient on average. The EAG also uses utilities derived from mapping PedsQL scores from study RM-493-023 to obtain baseline utilities using linear interpolation from [redacted] for BMI-Z >=4 to [redacted] for BMI-Z 0.0 – 1.0. All other assumptions in the EAG base-case are unchanged. Results are provided in the Addendum to the EAG report.
Company's base case following	Incremental QALYs: QALYs: [redacted]	Incremental costs: [redacted]	Please provide company revised base-case ICER	Note the companys calculation of undiscounted QALYs

technical engagement (or revised base case)	Undiscounted QALYs: [redacted]		£198 271	doesn't make a half-cycle correction. We adjusted the model to correct for this which gives a figure for undiscounted QALYs of [redacted].

Sensitivity analyses around revised base case

References

Forsythe E, Haws RM, Argente J, Beales P, Martos-Moreno G, Dollfus H*, et al.* Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results. *Orphanet Journal of Rare Diseases* 2023;**18**(1)

Forsythe E, Haws R, Argente J, et al. Quality of life in patients with Bardet-Biedl syndrome in a setmelanotide Phase 3 trial. *Obesity* 2021

Riazi A, Shakoor S, Dundas I, Eiser C, McKenzie SA. Health-related quality of life in a clinical sample of obese children and adolescents. *Health and Quality of Life Outcomes* 2010;**8**(1)

Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. *Pharmacoeconomics* 2014;**32**(7)

Obesity and hyperphagia (Bardet-Biedl syndrome) - setmelanotide

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation

Addendum to the Evidence Assessment Group Report

Produced by: Bristol Technology Assessment Group, University of Bristol
Date completed: 03/7/23

[redacted]

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Abbreviations

Abbreviation	Definition	Abbreviation	Definition
BBS	Bardet-Biedl syndrome	ICER	Incremental Cost Effectiveness Ratio
BMI	Body Mass Index	NICE	National Institute for Health and Care Excellence
BMI-Z	Body Mass Index Z score	NIHR	National Institute for Health and Care Research
CEAC	Cost-Effectiveness Acceptability Curve	PCAS	Placebo-Controlled Analysis Set
CS	Company Submission	PedsQL	Paediatric Quality of Life Inventory
EAG	Evidence Assessment Group	QALY	Quality-Adjusted Life Year
FAS	Full Analysis Set (as defined in company submission)	SAS	Safety Analysis Set

1 CLINICAL EFFECTIVENESS

The EAG has amended Tables 8 and 10 from the EAG report to reflect the additional information provided by the company at technical engagement.

Table 8 Efficacy results for Study RM-493-023 (List of outcomes based on CS, Tables 11 & 17) [Amended post technical engagement.]

Outcome	Comparison	Analysis	Proportion imputed data	Result	EAG comments	EAG risk of bias assessment
Primary outcomes:						
Proportion of patients aged ≥12 years who achieved at least 10% bodyweight reduction from baseline, after 52 weeks.	Single arm, no control group	Pivotal, FAS	[redacted]	Estimated proportion of patients aged ≥12 years achieved a ≥10% reduction in body weight after 52 weeks was [redacted] (n=28) (Table 23 of the CS).	Primary endpoint reported for the full trial population (BBS and AS patients) and BBS patients only. As the submission relates only to use of setmelanotide in BBS patients, results are only reported for BBS population. Not clear how many participants had their outcome value imputed.	Moderate+
Proportion of patients aged ≥18 years who achieved at least 10% bodyweight reduction from baseline after 52 weeks (post hoc)	Single arm, no control group	Pivotal, FAS	[redacted]	Estimated proportion of patients aged ≥18 years achieved a ≥10% reduction in body weight after 52 weeks was 46.7% (21.3, 73.4) 0.0003 (n=15) (Table 23 of the CS).	Primary endpoint reported for the full trial population (BBS and AS patients) and BBS patients only. As the submission relates only to use of setmelanotide in BBS patients, we present results only for this population. Not clear how many participants had their outcome value imputed.	Moderate+
Secondary outcomes:						
Mean percent change in body weight from baseline in patients	Single arm, no control group	Pivotal, FAS	[redacted] (may include participants with AS)	Change in bodyweight from 'active-treatment baseline' to 52 weeks was reported in Table 29 of the CS by pivotal patients aged	The prespecified endpoint used an age cut off for patients aged ≥12 years, however the results were reported in the CS using a cut off age	Not assessed

aged ≥12 years after ~52 weeks of treatment.				≥18 years. A reduction from baseline in body weight, compared with a reference value of 0% reduction, was reported with a mean weight loss at 52 weeks of -9.42kg and a mean percent change of -7.57% (n=15).	of ≥18 years (Risk of Bias assessed: moderate). Not clear how many participants had their outcome value imputed. Percent change in body weight is reported in the Haqq publication [13] in patients aged ≥12 years. However, this includes AS & BBS patients.	
Percent change in weekly average daily hunger score from baseline in patients aged ≥12 years after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	[redacted]	Reductions in weekly average percent change from active-treatment baseline to 52 weeks were reported for average hunger over 24 hour (mean [redacted]); most/worst hunger over 24 hours (mean 30.45) and morning hunger (mean [redacted]) in pivotal patients aged ≥12 years without cognitive impairment (n=14).	Clarification response A1 notes that hunger score is not a reliable clinical measure in BBS patients. The EAG notes that hyperphagia was not measured quantitatively or qualitatively in RM-493-023.	Not assessed
The proportion of patients aged ≥12 years reaching a daily hunger score reduction threshold of 25% after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	[redacted]	An estimated 57.1% of pivotal patients aged ≥12 years without cognitive impairment (n=14) reached the reduction threshold of ≥25% in weekly average of daily hunger score. When compared to a reference value of 0 it was shown to be statistically significant (p<0.0001, Table 28 of the CS).	Clarification response A1 notes that hunger score is not a reliable clinical measure in BBS patients. The EAG notes that hyperphagia was not measured quantitatively or qualitatively in RM-493-023.	Not assessed

Mean percent change in body weight from baseline in patients aged ≥12 years after ~14 weeks of treatment	Randomised, Placebo comparison	All, PCAS	[redacted]	Mean percent change in body weight was described in all patients (pivotal and supplemental) aged ≥18 years. A reduction in body weight from placebo-controlled period baseline to 14 weeks was shown in the setmelanotide treatment arm (n=10), when compared to the placebo arm (n=12). Mean percent change (kg) in the setmelanotide arm after 14 weeks was [redacted] versus [redacted] in the placebo arm [redacted].	The endpoint prespecified in the CS used an age cut off of patients aged ≥12 years, however the outcome was reported using a cut off age of ≥18 years. The Haqq *et al* published study report [13] does report this outcome for patients aged ≥12 years with a mean percent change in the setmelanotide arm of -3.7 (n=18) versus -0.2 in the placebo arm (n=18) (p=0.0019).	Low^
Mean percent change in weekly average of daily hunger score from baseline in patients aged ≥12 years after ~14 weeks of treatment	Randomised, Placebo comparison	All, PCAS	[redacted]	Greater reductions in the weekly average of daily hunger score were observed in the setmelanotide treatment group vs the placebo group from baseline to 14 weeks. Table 24 in the CS provides a summary of the results for most/worst hunger over 24 hours; average hunger over 24 hours and morning hunger.	Outcome reported for patients without cognitive impairment.	Low^
Exploratory/post hoc outcomes:						
Proportion of patients aged ≥12 achieving a ≥10% reduction in body weight or ≥15% reduction in BMI after ~52 weeks of treatment	Single arm, no control group	Pivotal, FAS	[redacted]	Not reported as a composite outcome in CS (≥15% reduction in BMI not reported).	EAG note that this outcome was not reported in the CS. Proportion of patients aged ≥12 achieving a ≥10% reduction in body weight was the primary efficacy outcome.	Not assessed
Change and % change of BMI Z-score in paediatric	Single arm, no control group	Pivotal, FAS	[redacted]	After 52 weeks of setmelanotide treatment a mean change in BMI Z-score of -0.75 points	Change in BMI Z-score was not reported by 6-11 or 6-16 age groups. But was reported for participants	Not assessed

patients after ~52 weeks of treatment by age group (6-11 years and/or 6-16 years)				(p=<0.0001) was reported in pivotal patients aged <18 years (n=14, Table 30 in the CS). Mean change over time is shown in Figure 10 of the CS. A 0.2-point reduction from baseline in BMI Z-score was reported in 85.7% of patients aged <18 years (n=14) and 71.4% achieved at least a 0.3-point reduction (n=14, Table 31 in the CS).	aged <18 years (Risk of Bias assessed: moderate). The rationale for the change is not described.	
Change in BMI after 52 weeks of treatment in patients aged <18 and ≥18 years	Single arm, no control group	Pivotal, FAS	[redacted]	A mean BMI change from active-treatment baseline of 4.22 kg/m2 and a mean percent change of 9.09% was reported in pivotal patients aged ≥18 years (n=12, Table 33 in the CS). A mean BMI change from active-treatment baseline of 3.36 kg/m2 and a mean percent change of 9.50% was reported in pivotal patients aged <18 years (n=14, Table 33 in the CS).	Not explicitly specified as an exploratory outcome in CS. Outcome data available for 14/16 (<18) and 12/15 (≥18 years)	Moderate+

+Assessed using Cochrane guidance on assessing risk of bias in uncontrolled before-after studies;[14] ^Assessed using risk of bias tool for RCTs, version 2 ("RoB 2")[12]

Active-treatment baseline = last measurement before the first dose of setmelanotide (i.e. week 0 for setmelanotide group, week 14 for the placebo group). AS = Alström syndrome, BBS = Bardet-Biedl syndrome, BMI = body mass index, CS = company submission, EAG = external assessment group; FAS= full analysis set; RoB = risk of bias.

Table 10: Risk of Bias in RM-493-23 open-label single-arm continuation study, for endpoints at 52 weeks, assessed by EAG for primary efficacy outcome; weight, BMI and BMI-z change from baseline; and post hoc outcomes used in the economic model. [Amended post technical engagement.]

	Risk of bias domains						**Overall risk of bias for the outcome**
Outcomes	Confounding	Selection of participants into the study	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result	
Primary efficacy endpoints:							
Proportion of BBS patients aged ≥12 years with a ≥10% reduction in body weight from active treatment baseline to 52 weeks setmelanotide treatment (pivotal FAS, CS Table 23, N=28, imputed: [redacted]	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding (applies to all listed outcomes): Moderate concerns for confounding due to lack of any control for confounding, but the differences in groups in weight reduction in the placebo-controlled period and in the later open-label period are somewhat reassuring. **Missing data**: Concerns about missing outcome data at 52 weeks. [redacted] missing outcomes have been imputed with baseline values (based on the new information provided in technical engagement). This conservative 'presumed treatment failure' approach to imputation is likely to bias the estimate towards the null. **Selective reporting:** No concerns for this outcome as it is consistently listed a pre-specified primary endpoint in the protocol, the published design paper [9], in the CS and the company trial [13].						
Subgroup: Proportion of BBS patients aged ≥18 years with a ≥10% reduction in body weight from active treatment baseline to 52 weeks setmelanotide treatment (pivotal FAS, CS Table 23, N=15, imputed: [redacted]	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding: as for primary endpoint, see above. **Missing data**: [redacted] missing outcomes have been imputed with baseline values for those participants. This 'presumed treatment failure' approach to imputation is likely to bias the estimate towards the null. ***Selective reporting** (applies to all outcomes denoted with *): Full protocol was made available at technical engagement along with the dates of protocol amendments, all of which occurred before the first efficacy analyses. The age-subgroup cut-off specified in the study protocol for most outcomes is <12 and ≥12 years, and the results for these pre-specified age subgroups are provided in the clinical study reports for RM-493-23. However, in the CS most outcomes were provided for age group cut-offs of <18 and ≥18 years instead. We have **assumed** that the age subgroup analyses using the 18-year-cut-off were produced specifically for the submission to NICE, to match the scope, although this was not explicitly stated. It is therefore unlikely that these new age subgroups were selected to be provided in the CS on the basis of the results.						
Weight, BMI and BMI-z change from baseline:							

Change and % change in body weight from baseline to 52 weeks setmelanotide treatment in Patients aged ≥18 years (pivotal FAS, CS Table 29, Figure 9, N=15, imputed: [redacted]	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding: as for primary endpoint, see above. **Missing data**: as for the previous endpoint, see above. ***Selective reporting:** See full explanation above, under the second listed outcome.						
Change and % change in BMI from baseline to 52 weeks of setmelanotide treatment in patients aged <18 and ≥18 years (pivotal FAS, CS Table 33, N=16 and 15, outcome data available for 14/16 and 12/15 respectively, no imputation performed)	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding: as for primary endpoint, see above. **Missing data**: 2/16 (13%) for <18 and 3/15 (20%) for ≥18 years old patients have missing outcomes, complete-case analysis, no imputation performed. ***Selective reporting:** See full explanation above, under the second listed outcome.						
Change in BMI Z-score from baseline to 52 weeks of setmelanotide treatment in patients aged <18 and years (pivotal FAS, CS Table 30, N=16, outcome data available for 14/16, no imputation performed)	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding: as for primary endpoint, see above. **Missing data**: 2/16 (13%) missing outcomes, complete-case analysis, no imputation performed. ***Selective reporting:** See full explanation above, under the second listed outcome.						
Outcomes informing the economic model:							
Proportions of patients aged <18 years achieving at least 0.2 and 0.3 point reduction in BMI Z-score from baseline after 52 weeks of setmelanotide treatment (pivotal FAS, CS Table 31, N=16, outcome data available for 14/16 for both outcomes, no imputation)	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
	Confounding: as for primary endpoint, see above. **Missing data**: 2/16 (13%) missing outcomes for both (0.2 and 0.3 point reduction) outcomes, complete-case analysis, no imputation performed. ***Selective reporting:** See full explanation above, under the second listed outcome.						
Post-hoc analysis: BMI shift data for individual patients aged ≥18 years who were classified as 52week responders (pivotal patients, CS Table 34, N=7; average responder shift was [redacted] BMI class)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: Analysis includes only participants considered responders. **Selective reporting:** Serious concerns for this unplanned post-hoc analysis in the responders-only subgroup. However, this may be appropriate for use in the economic model.						
Post-hoc analysis: BMI Z-score shift data for individual patients aged <18 years who were classified as 52week responders (pivotal patients, CS Table 35, N=12, average responder shift was [redacted] BMI Z-score class)	Moderate	Low	Low	Serious	Low	Serious	**Serious**
	Confounding: as for primary endpoint, see above. **Missing data**: Analysis includes only participants considered responders. **Selective reporting:** Serious concerns for this unplanned post-hoc analysis in the responders-only subgroup. However, this may be appropriate for use in the economic model.						

2 COST EFFECTIVENESS

2.1 EAG correction to companys updated scenario analyses

The company provided an updated base-case at technical engagement, with [redacted] carers per adult patient. They explored two scenarios in response to the EAGs Key Issues #9 and #10. However, as noted in the EAG response to the Companys Technical Engagement response, the calculations of the utilities used mappings for the average PedsQL score, rather than mapping each individual PedsQL score and then forming an average. Correcting this gives a utility of [redacted] for BMI-Z >= 4 rather than [redacted], which corresponds to a utility multiplier for non-obesity related comorbidity in scenario for Key Issue #10 of [redacted]. Table 2 shows the results for the Company updated base-case scenarios for Key Issues #9 and #10 for the paediatric population, with the corrected utilities. Table 3 and Table 4 show the same results for the mixed (60% paediatric, 40% adult) and adult populations respectively.

Table 2 Cost-effectiveness results for the Companys updated base-case, and corrected scenarios in response to Key Issues #9 and #10: paediatric population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case ([redacted] carers per adult patient)							
BSC	£117,404	3.97	1.31				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,641
Companys updated base-case, scenario in response to Key Issue #9:EAG Correction to Mapping							
BSC	£117,412	6.86	2.45				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,429
Companys updated base-case, scenario in response to Key Issue #10:EAG Correction to Mapping							
BSC	£117,037	4.73	1.53				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£187,989

Table 3 Cost-effectiveness results for the Companys updated base-case, and corrected scenarios in response to Key Issues #9 and #10: adult population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case ([redacted] carers per adult patient)							
BSC	£131,375	1.82	1.01				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,614
Companys updated base-case, scenario in response to Key Issue #9: EAG Correction to Mapping							
BSC	£130,986	4.05	2.19				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£195,319
Companys updated base-case, scenario in response to Key Issue #10: EAG Correction to Mapping							
BSC	£130,301	2.62	1.43				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£216,982

Table 4 Cost-effectiveness results for the Companys updated base-case, and corrected scenarios in response to Key Issues #9 and #10: mixed 60% paediatric and 40% adult population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case ([redacted] carers per adult patient)							
BSC	£122,993	3.11	1.19				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£204,894
Companys updated base-case, scenario in response to Key Issue #9:EAG Correction to Mapping							
BSC	£122,841	5.73	2.34				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,161
Companys updated base-case, scenario in response to Key Issue #10:EAG Correction to Mapping							
BSC	£122,343	3.89	1.49				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194,671

2.2 Exploratory and sensitivity analyses undertaken by the EAG

All of the EAGs scenario analyses were applied to the company's updated base-case model received by the EAG on 09/06/23 following technical engagement.

The EAG conducted the following scenarios:

- Scenario 1: Initial severity of hyperphagia where 60% of patients have severe hyperphagia, and 40% have moderate hyperphagia.
- Scenario 2: Treatment discontinuation rate of 2%.
- Scenario 3: Treatment effect on hyperphagia with [redacted] pf patients moving to mild, and [redacted] to moderate.
- Scenario 4: Treatment effect on BMI-Z where paediatric patients who respond to treatment achieve a reduction in BMI-Z / BMI class of [redacted].
- Scenario 5: Number of carers for adults set to (a) 0.5 carers, (b) the company has updated their base-case to include [redacted] carers, and so the EAG have not included their Scenario 5b in this Addendum.
- Scenario 6: BBS utility multiplier to different values of (a) 0.9 and (b) 0.7.
- Scenario 7: Monitoring costs for setmelanotide reflect updated physician monitoring visit costs and an additional visit in years 2+.
- Scenario 8: Waning of treatment effect assumed to be 1%.
- Scenario 9: Setmelanotide response rate of 80%.

The results from the EAGs scenario analyses are shown for the paediatric population in Table 5 and for the mixed (60% paediatric, 40% adult) population in Table 6**Error! Reference source not found.**. All results shown are from a probabilistic analysis.

Not all scenarios can be combined together, we therefore show the effect of combining scenarios 2, 3, 4, 6a, 7, 8, and 9.

Table 5 EAGs additional scenario analyses applied to the Company's updated base case model paediatric population (probabilistic results displayed)

No.	Scenario	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
0	Company's updated base case (probabilistic)	[redacted]	[redacted]	[redacted]	£197,641
1	Initial severity of hyperphagia	[redacted]	[redacted]	[redacted]	£234,346
2	Treatment discontinuation	[redacted]	[redacted]	[redacted]	£196,907
3	Treatment effect on hyperphagia	[redacted]	[redacted]	[redacted]	£223,296
4	Treatment effect on BMI-Z	[redacted]	[redacted]	[redacted]	£213,230
5a	Number of carers for adults = 0.5	[redacted]	[redacted]	[redacted]	£204,189
5b	Number of carers for adults = [redacted]	Company have incorporated [redacted] adult carers in their updated base-case			
6a	BBS utility multiplier 0.9	[redacted]	[redacted]	[redacted]	£181,684
6b	BBS utility multiplier 0.7	[redacted]	[redacted]	[redacted]	£219,423
7	Monitoring costs for setmelanotide	[redacted]	[redacted]	[redacted]	£197,992
8	Waning of treatment effect	[redacted]	[redacted]	[redacted]	£204,469
9	setmelanotide response rate	[redacted]	[redacted]	[redacted]	£199,222
All	2 + 3 + 4 + 5b + 6a + 7 + 8 + 9	[redacted]	[redacted]	[redacted]	£222,156

Table 6 EAGs additional scenario analyses applied to the Company's updated base case model mixed 60% paediatric 40% adult population (probabilistic results displayed)

No.	Scenario	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
0	Company's updated base case (probabilistic)	[redacted]	[redacted]	[redacted]	£204,894
1	Initial severity of hyperphagia	[redacted]	[redacted]	[redacted]	£244,038
2	Treatment discontinuation	[redacted]	[redacted]	[redacted]	£205,095
3	Treatment effect on hyperphagia	[redacted]	[redacted]	[redacted]	£232,406
4	Treatment effect on BMI-Z	[redacted]	[redacted]	[redacted]	£218,105
5a	Number of carers for adults = 0.5	[redacted]	[redacted]	[redacted]	£213,920
5b	Number of carers for adults = [redacted]	Omitted. Company have incorporated [redacted] adult carers in their updated base-case			
6a	BBS utility multiplier 0.9	[redacted]	[redacted]	[redacted]	£188,157
6b	BBS utility multiplier 0.7	[redacted]	[redacted]	[redacted]	£228,382
7	Monitoring costs for setmelanotide	[redacted]	[redacted]	[redacted]	£205,467
8	Waning of treatment effect	[redacted]	[redacted]	[redacted]	£211,949
9	setmelanotide response rate	[redacted]	[redacted]	[redacted]	£207,582
All	2 + 3 + 4 + 5b + 6a + 7 + 8 + 9	[redacted]	[redacted]	[redacted]	£228,333

2.3 EAG updated base-case

The EAG have updated their base-case in response to the additional information provided by the Company at Technical Engagement. The EAGs base-case now includes [redacted] carers per adult patient, in line with the companys updated base-case. The EAG prefer the approach to baseline utilities presented in the

companys response to Key Issue #9, as this avoids the need for a non-obesity related BBS comorbidity utility multiplier. However, as discussed above, the EAG use the corrected mappings, where the individual PedsQL scores from study RM-493-023 are mapped and then averaged. This gives an average utility of [redacted] for the 4 patients with BMI-Z >= 4. The company uses the utility from Riazi's "healthy population" for BMI-Z category 0.0 – 1.0 of [redacted] and a linear interpolation for other BMI-Z categories. The EAG believes that the company has made the same error in the calculation of the utilities from Riazi, and in the absence of the data to correct for this, the EAG has calculated the utility for the 1 individual in the 0.0 – 1.0 category from study RM-493-023, giving a utility of [redacted]. The EAG then uses linear interpolation for the other BMI-Z categories (Table 7).

Table 7 Baseline utility values by BMI-Z category in the EAG updated base-case

BMI Z	Utility
0.0-1.0	[redacted]
1.0-2.0	[redacted]
2.0-2.5	[redacted]
2.5-3.0	[redacted]
3.0-3.5	[redacted]
3.5-4.0	[redacted]
⩾4.0	[redacted]

The EAG's preferred assumptions are:

1. 2% discontinuation rate
2. Treatment effect on hyperphagia with [redacted] moving to mild and [redacted] to moderate
3. Treatment effect on BMI-Z of a [redacted]-level reduction in BMI-Z class for the paediatric BBS population
4. Secondary/tertiary care costs for monitoring visits in weight-management clinics setmelanotide group in the first and subsequent years
5. Baseline utilities from the PedsQL scores from study RM-493-023 using Khan's algorithm for the mapping, and linear interpolation between the values for BMI-Z >=4 and BMI-Z 0.0 – 1.0.

The results for the for the EAGs preferred assumptions are shown for the paediatric population in
Table 8, for the mixed (60% paediatric, 40% adult) population in Table 9 , and for the adult population in

Table 10.

Table 8 Cost-effectiveness results for the EAGs updated base-case: paediatric population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	£117,404	3.97	1.31				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,641
+ 2% discontinuation rate (assumption 1)							
BSC	£116,872	3.93	1.28				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£195,611
+ treatment effect on hyperphagia (assumptions 1 + 2)							
BSC	£116,988	3.72	1.20				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£219,365
+ treatment effect on BMI-Z (assumptions 1 + 2 + 3)							
BSC	£117,636	3.84	1.25				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£235,157
+ secondary care monitoring costs (assumptions 1 + 2 + 3 + 4)							
BSC	£117,374	3.82	1.23				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£235,857
+ PedsQL utilities (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	£117,453	6.86	2.47				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£203,784

Table 9 Cost-effectiveness results for the EAGs updated base-case: mixed 60% paediatric and 40% adult population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	£122,993	3.11	1.19				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£204,894
+ 2% discontinuation rate (assumption 1)							
BSC	£122,534	3.06	1.16				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£203,589
+ treatment effect on hyperphagia (assumptions 1 + 2)							
BSC	£122,594	2.88	1.08				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,242
+ treatment effect on BMI-Z (assumptions 1 + 2 + 3)							
BSC	£122,831	3.03	1.15				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,532
+ secondary care monitoring costs (assumptions 1 + 2 + 3 + 4)							
BSC	£122,682	3.00	1.13				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,309
+ PedsQL utilities (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	£122,870	5.71	2.35				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,457

Table 10 Cost-effectiveness results for the EAGs updated base-case: adult population (probabilistic results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	£131,375	1.82	1.01				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,614
EAG updated base-case							
BSC	£130,995	3.99	2.16				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222,857

3 QALY Weighting

In the companys updated base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the EAG preferred base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). Whilst all these figures are uncertain and based on strong assumptions, the EAG considers that it is plausible that a QALY weighting may apply in the paediatric population. The EAGs base-case estimate would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

4 References

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Thank you for providing your views on this technology and its possible use in the NHS. You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised

data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

NICE National Institute for Health and Care Excellence

Part 1: Treating Bardet-Biedl syndrome and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Elizabeth Forsythe
2. Name of organisation	National Health Service, Guys and St Thomas Hospitals, National Bardet-Biedl syndrome services Asked by Rhythm Pharmaceuticals to provide expert advice for this meeting
3. Job title or position	Consultant in Clinical Genetics
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Bardet-Biedl syndrome? ☒ A specialist in the clinical evidence base for Bardet-Biedl syndrome or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No

8. What is the main aim of treatment for Bardet-Biedl syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Bardet-Biedl syndrome is a complex multisystem condition. Overall the main difficulties patients and parents worry about are visual deterioration,obesity/ hyperphagia and intellectual disability/ behaviour challenges. The main aims would be to stop visual deterioration, prevent obesity and hunger and improve intellectual capacity.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	For weight management the aim would be to get a BMI in the healthy range and for those patients with hyperphagia to reduce this to a level that does not interfere with activities of daily living/ concentration at school/ work. A clinically significant treatment response should be greater than that which can be achieved with diet and exercise intervention (around 10% weight loss). Hunger reduction is harder to quantify, but a subjective reduction so that those with hyperphagia are less disturbed at school/ work/ sleep would be clinically significant effect.
10. In your view, is there an unmet need for patients and healthcare professionals in Bardet-Biedl syndrome?	Yes
11. How is Bardet-Biedl syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Symptomatic treatment. Patients attend the national Bardet-Biedl syndrome clinics in London and Birmingham 18 monthly. They see a team including a geneticist, endocrinologist, dietitian, nephrologist, psychologist and member of the support team. In addition the children see a speech and language therapist. Weight and hunger is primarily addressed by the endocrinologist and dietitian. Management is supportive. Some of the patients who are also diabetic are on semaglutide. Some patients have additional dietetics/ endocrine support in the community. The care setup is the same in all four centres (an adult centre and paediatric centre in each location). There are some minor differences in approach, but broadly the care si the same. Setmelanotide would be an adjunct to the care pathway for obesity/ hunger in place already.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	We currently have limited treatment options for obesity and hunger in Bardet-Biedl syndrome. Setmelanotide would be the only MC4R agonist available for our patients. GLP1 agonists (liraglutide and semaglutide) are not widely used in BBS yet so we do not understand the effect in BBS at this point. The MC4R pathway is abrogated in BBS which makes Setmelanotide an attractive therapeutic candidate but it may well be that GLP1 agonists will work equally well or better in BBS. In order to monitor the effect and also ensure supply I would suggest that setmelanotide should initially be prescribed from the specialist BBS clinics. It makes most sense for the drug to be delivered in a prefilled syringe so that it is accessible to patients with sight impairment (as is the case for the majority of patients) This depends somewhat on how the drug is delivered, if not in pre-filled syringes then more training/ guidance/ help for patients is required. If in pre-filled syringes then in the first instance there should be funding for a clinician who can answer questions on delivery/ side effects.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, indirectly if weight is improved then there will be fewer sequelae related to obesity and this would affect life span. Yes, hyperphagia and obesity significantly affect quality of life in these patients, if this can be improved then quality of life is improved.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I would expect Setmelanotide to be more effective in patients with abrogated MC4 pathway such as people with Bardet-Biedl syndrome.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	It will be an additional tool for managing obesity and hyperphagia. The main challenge is around drug delivery. Need to ensure it can be used by visually impaired individuals.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No formal rules. Clinical judgement. Patients with obesity would be eligible to start the technology.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Hyperphagia needs to be assessed.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes in that it is an anti-obesity drug that works specifically on the MC4 pathway which is the pathway that is abrogated in BBS. It addresses the unmet need to manage obesity and hyperphagia in patients with BBS. It remains to be seen if a similar effect can be achieved with GLP1 agonists or setmelanotide plus a GLP1 agonist could have an additive effect.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nausea/ abdominal issues are transient. Hyperpigmentation was noticeable in patients and commented on. Level of hyperpigmentation varies. If significant may make some patients self-conscious.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The most important outcomes are weight change and change in hunger. Other important outcomes relate to change in metabolic syndrome indicators. All of these were measured in the trials. No additional adverse effects have become apparent.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	Comparable effects seen in my patients on clinical trial and those reported by others and overall.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering Bardet-Biedl syndrome and this treatment? Please explain if you think any groups of people with Bardet-Biedl syndrome are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	The main issue in terms of equity is ensuring that this drug is accessible to those with visual impairment. In its initial form patients had to extract the drug from a vial and ensure the correct dose was extracted. This is not possible for those with visual impairment so only patients with carers who were able to attend daily were able to take part in the trial. In order to make this accessible to the many BBS patients with visual impairment who live (at least partly) independently this drug needs to be delivered in a way that is accessible to them (eg prefilled syringes/ once weekly)

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
25. Topic specific questions What proportion of people with Bardet-Biedl syndrome have severe hyperphagia in clinical practice and how is this identified?	In my opinion this is 50-60%. We do not formally measure this. It is a ballpark figure based on 10+ years experience in the clinic.
Are clinical experts aware of any credible prevalence estimates for severe hyperphagia?	No formal assessments/ published prevalence to my knowledge.
Would you expect differences in treatment options and outcomes for people with Bardet-Biedl syndrome by geological location?	No
Would you expect weight and hunger fluctuations over time in people taking best supportive care?	No
What is the relationship between hunger (as measured in the trials) and hyperphagia?	Significant relationship. Most obvious in children. My impression is that adults with better cognitive functions seem to learn to manage it to an extent.
How are hyperphagia and BMI associated in Bardet-Biedl syndrome obesity? Would you expect:	My impression is that hyperphagia and BMI correlate but other factors are highly significant -cognitive abilities in adults and parental resources in children.

Clinical expert statement

• The level of hyperphagia to correlate with the severity of the BMI? • reductions in BMI to improve hyperphagia?	
Is it clinically plausible that setmelanotide's treatment effect would wane over time?	Yes
What is the quality-of-life impact for non-obesity related Bardet-Biedl syndrome comorbidities? Are you aware of any data for Bardet-Biedl syndrome that could inform the utility multiplier in the model?	Significant quality of life impact caused by sight impairment. I am not aware of data that would specifically inform the utility multiplier in the model.
• How does Bardet-Biedl syndrome affect the quality of life of carers? On average, how many carers would you expect for a) adults and b) children with Bardet-Biedl syndrome?	Yes it does. See abstracts at recent conferences on effect on carers. Carers for adults: usually 1 or 2. For children usually 2.
• Would bariatric surgery be used in this population? • Would semaglutide be used to treat obesity in people with Bardet-Biedl syndrome?	Bariatric surgery has been used in a few. The effect is usually not satisfactory. Semaglutide and other drugs potential coming on to the market such tirzepatide may be useful in BBS. It may also be that combination therapy with semaglutide would work well.
In terms of outcomes, how does Bardet-Biedl syndrome obesity differ from: • General obesity? • Other genetic deficiencies that result in obesity (such as LEPR or POMC deficiency, Alström syndrome, Smith-Magenis syndrome and Carboxypeptidase E syndrome)?	Obesity in BBS differs from general obesity in that BBS patients appear to have a much stronger hyperphagia drive. They may also well be more predisposed to metabolic syndrome. Of note the cholesterol profile is often abnormal in slim children. Outcomes may be similar to other genetic obesities syndromes but I am not aware of any published data that compares outcomes.
In what setting would setmelantode be monitored (primary care, local secondary care or specialist centres)?	Specialist centres ideally.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Bardet-Biedl syndrome is a rare genetic cause of obesity and hyperphagia
Management so far has been supportive
Setmelanotide is an MC4R agonist
In clinical trials Setmelanotide has had a clinically significant effect on obesity and hunger in patients with BBS
It remains to be seen if setmelanotide has a superior effect of weight and hunger over GLP1 agonists such as semaglutide or if combination therapy would have an additive effect

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Thank you for providing your views on this technology and its possible use in the NHS. You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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Thank you for your time.

Part 1: Treating Bardet-Biedl syndrome and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dimitri Pournaras on behalf of the British Obesity and Metabolic Surgery Society
2. Name of organisation	British Obesity and Metabolic Surgery Society (BOMSS)
3. Job title or position	Consultant Bariatric Surgeon and BOMSS/RCS Research Lead
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with Bardet-Biedl syndrome? ☒ A specialist in the clinical evidence base for Bardet-Biedl syndrome or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for Bardet-Biedl syndrome?	In the context of obesity, weight loss maintenance and reduction of the risk associated with obesity and obesity associated disease.

Clinical expert statement

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	5% weight loss is clinically significant. !0% weight loss is even more beneficial. Weight gain prevention without weigh loss is also clinically important in the context of this chronic condition.
10. In your view, is there an unmet need for patients and healthcare professionals in Bardet-Biedl syndrome?	Absolutely. There is currently no pharmacologic treatment.
11. How is Bardet-Biedl syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Centralised treatment in four centres with clear guidance. The pathway is well defined.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Setmelanotide can be used in addition to current multidisciplinary obesity care focused on weight gain prevention, weight loss and weight loss maintenance in specialist centres.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Weight loss maintenance mediated with setmelanotide in the context of Bardet-Biedl syndrome is likely to reduce risk of type 2 diabetes, cardiovascular risk, cancer risk and ultimately increase life expectancy. It is also likely to lead to improvement in overall quality of life and function as these measures are significantly affected by obesity. Particular focus should be placed on control of hyperphagia, a debilitating symptom. Control of hyperphagia even in the absence of clinically meaningful weight loss would be impactful on quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Early treatment at relatively lower BMI may be more effective than very high BMI extrapolating this from obesity care in general.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be easier to achieve weight loss as opposed to obesity care based on lifestyle intervention only.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A response to treatment will be a marker. This should include hunger, hyperphagia assessment and quality of life in addition to the weight loss/reduction of BMI. In the context of weight gain, weight stability can also be considered as a successful outcome.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Improvement in hunger is important for quality of life in any person living with obesity. In the context of Bardet-Biedl syndrome control of hyperphagia in addition to hunger should be considered in its own merit and independently of weight loss.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Effective of obesity care associated with control of hunger and hyperphagia is desperately needed. Setmelanotide treatment will be a step change.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The hyperpigmentation may affect negatively quality of life, but this should be balanced against the overall improvement in quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

23. How do data on real-world experience compare with the trial data?	As the treatment will be delivered in highly specialised centres of excellence the difference between clinical trials and real world is very narrow.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering Bardet-Biedl syndrome and this treatment? Please explain if you think any groups of people with Bardet-Biedl syndrome are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	People living with obesity experience high levels of stigma. This is increased further by the additional aspects of Bardet-Biedl Syndrome. Access to effective care is urgently needed for individuals with the condition. I do not see any other issues.

Find more general information about the Equality Act and equalities issues here.	
25. Topic specific questions What proportion of people with Bardet-Biedl syndrome have severe hyperphagia in clinical practice and how is this identified?	Unable to define in view of the small numbers in our practice. History and scores can aid the diagnosis.
Are clinical experts aware of any credible prevalence estimates for severe hyperphagia?	Personally, not aware of an estimate.
Would you expect differences in treatment options and outcomes for people with Bardet-Biedl syndrome by geological location?	The social environment may have an effect.
Would you expect weight and hunger fluctuations over time in people taking best supportive care?	The impact of lifestyle interventions is usually more effective at the time of intervention with an expected weight regain afterwards. Hunger would be become worse during the intervention and this would continue at the end of the dietary intervention.
What is the relationship between hunger (as measured in the trials) and hyperphagia?	Hunger is a symptom that drives hyperphagia. Lack of satiety which is different from hunger is also part of this interaction and drives hyperphagia. Control of hyperphagia could happen without control of hunger but is likely to increase hunger. Appropriate control of hunger and hyperphagia will have the optimal impact and will lead to reduction of BMI with good quality of life.
How are hyperphagia and BMI associated in Bardet-Biedl syndrome obesity? Would you expect: • The level of hyperphagia to correlate with the severity of the BMI? • reductions in BMI to improve hyperphagia?	Improvement in obesity care improves hyperphagia and reduces BMI. Effective obesity interventions such as setmelanotide achieve this at the same time. Lifestyle interventions usually increase hunger at the time of intervention even if hyperphagia is controlled and BMI is reduced. This effect is enhanced at the end of the intervention.
Is it clinically plausible that setmelanotide's treatment effect would wane over time?	Most obesity interventions demonstrate fatigue over time. Should also point out that control of hyperphagia is an important outcome beyond weight loss maintenance and BMI reduction as this would impact positively quality of life independent of weight loss.

What is the quality-of-life impact for non-obesity related Bardet-Biedl syndrome comorbidities? Are you aware of any data for Bardet-Biedl syndrome that could inform the utility multiplier in the model?	Not aware of any data.
• How does Bardet-Biedl syndrome affect the quality of life of carers? On average, how many carers would you expect for a) adults and b) children with Bardet-Biedl syndrome?	
• Would bariatric surgery be used in this population? • Would semaglutide be used to treat obesity in people with Bardet-Biedl syndrome?	Bariatric surgery has been used in a very small number of individuals. A recent review included 7 patients. The results are variable, with an inferior response and less durable outcomes in the long term.
In terms of outcomes, how does Bardet-Biedl syndrome obesity differ from: • General obesity? • Other genetic deficiencies that result in obesity (such as LEPR or POMC deficiency, Alström syndrome, Smith-Magenis syndrome and Carboxypeptidase E syndrome)?	It is a subset of obesity. The response to conventional treatment options such as lifestyle modifications, pharmacotherapy and bariatric surgery is significantly inferior to the population.
In what setting would setmelantode be monitored (primary care, local secondary care or specialist centres)?	Specialist centres

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is an urgent and unmet need for safe and effective obesity care in the UK and globally.
Setmelanotide is a safe and effective treatment for individuals with Bardet-Biedl Syndrome.
The treatment is acceptable by patients and carers.
There is an improvement in quality of life due to symptom control, reduction in BMI and improvement in function.
Hunger and hyperphagia control are very important and the impact is beyond the associated weight loss maintenance and reduction in BMI.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Thank you for agreeing to give us your views on setmelanotide and its possible use in the NHS. Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

Information on completing this form

In part 1 we are asking you about living with the condition or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Monday 3 July 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

NICE National Institute for Health and Care Excellence

Part 1: Living with Bardet-Biedl syndrome or caring for a patient with Bardet-Biedl syndrome

Table 1 About you, the condition, current treatments and equality

1. Your name	MRS DANIELLE THOMAS
2. Are you (please tick all that apply)	☒ A patient with Bardet-Biedl syndrome? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Bardet-Biedl syndrome? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	BARDET BIEDL SYNDROME UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Bardet-Biedl syndrome? **If you are a carer (for someone with Bardet-Biedl syndrome) please share your experience of caring for them**	I HAVE ALWAYS HAD MILD LEARNING DIFFICULTIES WHICH IMPACTED ON MY DAILY LIFE ESPECIALLY WHEN YOUNGER. I HAD SUPPORT FROM THE AGE OF 5 THROUGHOUT SCHOLL, COLLEGE AND UNIVERSITY. I STILL CAN GET QUITE EMOTIONAL AND FIND CHANGE VERY DIFFICULT TO DEAL WITH. I HAVE ALWAYS HAD AN ISSUE WITH MY WEIGHT, AND HAVE ALWAYS HAD PORTION AND HUNGER CONTROL ISSUES BLADDER ISSUES, WHICH HAVE BEEN ONGOING AND QUITE EMBASRASSING AT TIMES, SO HAS AN EFFECT ON MY DAILY LIVING CONSTANT BACK PAIN DUE TO ARTHRITIS IN THE SPINE, SCOLIOSIS AND BULGING DISCS. PROSASIS IN MY HEAD AND BODY, AND WHEN STRESSED BECOMES MUCH WORSE. HIDRANITIS CAUSING PAINFUL BOILS CHRONIC FATIGUE, SO HAVE TO BE CAREFUL TO NOT OVERLOAD MYSELF WITH TOO MANY ACTIVITIES EVEN WITH ALL THE ABOVE I HAVE LEARNT TO COPE AND GET ON WITH MY LIFE, EVEN WHEN SOME DAYS ARE BETTER THAN OTHERS FROM A FAMILY MEMBER'S PERSPECTIVE, IT IS AN ONGOING WORRY ABOUT THE FUTURE FOR YOU CHILD/ADULT, AND THE FIGHT TO MAKE SURE THEY GET ALL THE HELP AND TREATMENT THEY DESERVE TO MAKE THEIR LIVES FULLFILLED

7a. What do you think of the current treatments and care available for Bardet-Biedl syndrome on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	AT THE MOMENT THE BEST TREATMENT AVIALBLE FOR BBS IS THE MULTI DISCIPLINARY CLINICS, WITH SPECIALISED DOCTORS THAT NOW HAVE THE EXPERIENCE OF HELPING BBS PATIENTS. OTHER THAN THE CLINIC, MANY DOCTORS DO NOT UNDERSTAND THE SYNDROME AND FIND IT DIFFICULT TO TREAT. NOT AWARE OF OTHER PEOPLE'S TREATMENT
8. If there are disadvantages for patients of current NHS treatments for Bardet-Biedl syndrome (for example, how setmelanotide is given or taken, side effects of treatment, and any others) please describe these	THERE ARE NO CURRENT TREATMENTS AVAILABLE ON THE NHS
9a. If there are advantages of setmelanotide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does setmelanotide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a** **I LOST 10% OF MY BODY WEIGHT.** **FELT CONSIDERABLY LESS HUNGRY, PORTION CONTROL WAS BETTER, AND FOR ME I DIDN'T EVEN WANT DESSERT AFTER A MEAL.** **I HAD MORE ENERGY, MY MOOD WAS GOOD, AND THE CHRONIC FATIGUE FELT MORE UNDER CONTROL.** **I HAD MORE CONFIDENCE, AND FELT BETTER GENERALLY** **I SUFFER FROM HIDRANITIS WITH LARGE BOILS, AND PSORIASIS, BUT WHILE ON THE TRAIL THESE CLEARED. NORMALLY THESE CAN MAKE ME FEEL QUITE UNWELL WHEN THE ARE ACTIVE. IT MADE ME WORRY LESS ABOUT THESE.** **9b** **NOT FEELING HUNGRY AND CONSTANTLY THINKING ABOUT FOOD** **LOSING WEIGHT AND FEELING HAPPY IN MYSELF** **FEELING MORE CONFIDENT, AND WELL MYSELF** **BETTER SKIN, WHICH MEANS YOU AREN'T SO SELF CONSCIOUS**

	9c
10. If there are disadvantages of setmelanotide over current treatments on the NHS please describe these. For example, are there any risks with setmelanotide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	HAVING TO DRAW UP SUCH A SMALL AMOUNT OF THE DRUG DAILY IN A SYRINGE AND HAVING TO INJECT DAILY. MY EYESIGHT AT THE MOMENT IS OK, BUT VERY DIFFICULT FOR A BLIND PERSON TO DO THIS INDEPENDETLY WHEN I STOPPED THE TRAIL OF THIS DRUG, THE HUNGER RETURNS AND WEIGHT GOES BACK ON. MOOD CHANGED AND SKIN CONDITIONS RETURNED
11. Are there any groups of patients who might benefit more from setmelanotide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	ALL PATIENTS WITH BBS WOULD BENEFIT FROM THIS, AND WOULD CHANGE THEIR LIFE FOR THE BETTER
12. Are there any potential equality issues that should be taken into account when considering Bardet-Biedl syndrome and setmelanotide? Please explain if you think any groups of people with Bardet-Biedl syndrome are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I FEEL THERE ARE NO EQUALITY ISSUES WITH BBS PATIENTS UNDER THE CARE OF THE CLINICS

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	NO
14. Topic specific questions *Please describe your experience of hyperphagia?*	
What outcomes are important to patients?	BETTER QUALITY OF LIFE THROUGH LOSING WEIGHT, HELPS ANY ISSUES CONNECTED TO OVERWEIGHT PROBLEMS
How would patients define a positive response to setmelanotide?	FELT CONSERABLY BETTER IN HEALTH AND MOOD WHILE TAKING THE DRUG.
If you, or someone you care for has taken setmelanotide, how did this affect their hunger and weight?	MY HUNGER WAS CONSIDERABLY LESS AND DID NOT THINK ABOUT FOOD ALL THE TIME I LOST 10% OF MY BODY WEIGHT SO FELT MORE CONFIDENT
How do non-obesity related comorbidities affect the quality of life for someone with Bardet-Biedl syndrome?	UNSURE
How does Bardet-Biedl syndrome affect the quality of life of carers?	CONSTANT WORRY ABOUT THEIR HEALTH AND WELL BEING
On average, how many people are involved in caring for someone with Bardet-Biedl syndrome? Does this differ by age?	PARENTS, OR SPOUSES, AND DOES NOT DIFFER WITH AGE

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- BETTER QUALITY OF LIFE, MORE CONFIDENT, HAPPIER AND FELT HEALTHIER
- LESS HUNGRY, AND DIDN'T CONSTANTLY THINK ABOUT FOOD
- LOST 10% OF MY BODY WEIGHT, SO FELT HAPPIER ABOUT MYSELF
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome [ID3947]

Thank you for agreeing to give us your views on setmelanotide and its possible use in the NHS. Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

Information on completing this form

In part 1 we are asking you about living with the condition or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Monday 3 July 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Part 1: Living with Bardet-Biedl syndrome or caring for a patient with Bardet-Biedl syndrome

Table 1 About you, the condition, current treatments and equality

1. Your name	Angela Scudder
2. Are you (please tick all that apply)	☐ A patient with Bardet-Biedl syndrome? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with Bardet-Biedl syndrome? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	BBSUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Bardet-Biedl syndrome? **If you are a carer (for someone with Bardet-Biedl syndrome) please share your experience of caring for them**	My son (17yrs) has BBS – The hyperphagia part of BBS is the part that has the most impact on his and our lives. This is an unmet need in his EHCP and his other medical care plans. Everybody including family, friends and professionals' does not understand the effect this has on his emotional wellbeing, how much it triggers behaviours, socially isolates him and efforts his life choices. We must plan every event around food – food is his biggest motivator and his worst enemy it really is that controlling for him. Managing this behaviour is exhausting.
7a. What do you think of the current treatments and care available for Bardet-Biedl syndrome on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**The MDT clinic are amazing, talking to consultants and other health care professional that really understanding.**
8. If there are disadvantages for patients of current NHS treatments for Bardet-Biedl syndrome (for example, how setmelanotide is given or taken, side effects of treatment, and any others) please describe these	As a parent it would be easier if the delivery was in pill form or even an epipen.
9a. If there are advantages of setmelanotide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	**Setmelanotide would allow a person with BBS to enjoy and be included in live without being judged for being the person who is the over eater.** **They will be more focused in education and the workplace, leading to better live outcomes.**

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does setmelanotide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of setmelanotide over current treatments on the NHS please describe these. For example, are there any risks with setmelanotide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from setmelanotide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with a cognitive impairment I believe would benefit more due to not understanding fully about healthy eating. My Son reports he is eating healthy because there is salad and vegetables on his plate however the rest of the meal may be an unhealth choice and he will still want pudding! Patients with cultural and religious believes would also benefit, for many they will live and are cared for by aging relatives that do not understand their need.
12. Are there any potential equality issues that should be taken into account when considering Bardet-Biedl syndrome and setmelanotide? Please explain if you think any groups of people with Bardet-Biedl syndrome are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	People with BBS can be exploited when others realise how much food motives them. Having some control over their hyperphagia will lead to an individual making better live choices and of course leading to better health outcomes.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Every parent who has a disabled child will worry about what happens to them when they are no longer alive/able to care/advocate for them. When you have a BBS child/adult you know people will consider their vision, kidneys, and other health need. They will reduce their diet but never consider the impact of hyperphagia on their everyday live. Without drugs like Setmelanotide to control hyperphagia I fear what will happen when I an no longer here!
14. Topic specific questions *Please describe your experience of hyperphagia?*	Always feeling hungry.
What outcomes are important to patients?	Not having Hyperphagia controlling there live
How would patients define a positive response to setmelanotide?	Not thinking about food all the time and weight loss.
If you, or someone you care for has taken setmelanotide, how did this affect their hunger and weight?	N/A
How do non-obesity related comorbidities affect the quality of life for someone with Bardet-Biedl syndrome?	Visual Impairment has a devastating effect both physically and emotionally.

How does Bardet-Biedl syndrome affect the quality of life of carers?	Caring for someone with BBS is very demanding - dealing with their personal care, emotions, weight gain, loss of vision, constant and deteriorating health needs, and behaviours.
On average, how many people are involved in caring for someone with Bardet-Biedl syndrome? Does this differ by age?	Yes, this dose differ with age, a child/young person will need there parents/household to care for them longer then a child/young person with out BBS. Support in school will be needed for the whole school day not just in the classroom – support will be needed during lunch and break times, PE and trips. Normally SEN transport is needed or parent to drop and pick up. Adults, need support with independent or supported living. Guiding skills. Health needs.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Hyperphagia is Real! To many people believe its just hunger that we all feel from time to time!
- Hyperphagia should be recognized the same as other medical conditions.
- Hyperphagia is both Physically and mentally painful for a person with BBS.
- We need to met the unmet need of Hyperphagia.
- Hyperphagia effects the whole family.

Thank you for your time.

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