NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome in people 6 years and over (review of HST31)

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using setmelanotide in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers). The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2026

Note that this document is not NICE's final guidance on setmelanotide. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using setmelanotide in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 07 August 2026
- Second evaluation committee meeting: 20 August 2026
- Details of the evaluation committee are given in section 5

1 Recommendations

1.1 Setmelanotide can be used as an option to treat obesity and hyperphagia in genetically confirmed Bardet-Biedl syndrome (BBS) in people aged 6 to 17 years. These people can carry on having setmelanotide as adults until they need to stop. Setmelanotide can only be used if the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with setmelanotide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

What this means in practice

Setmelanotide must continue to be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option.

There is enough evidence to show that setmelanotide provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

This evaluation reviews the evidence for setmelanotide for treating obesity and hyperphagia in BBS (see NICE highly specialised technology guidance 31, from now HST31). The discussion for this review is mainly about setmelanotide for adults who have not started the drug before age 18 years, for whom setmelanotide was not recommended in HST31. The recommendations for people starting treatment aged

6 to 17 years, and carrying on having it as adults, are no different from those in HST31.

Usual treatment for obesity and hyperphagia for adults with BBS (who have not started setmelanotide before age 18 years) is best supportive care. This includes dietary restrictions and lifestyle changes, including exercise, to manage symptoms. Liraglutide, semaglutide and tirzepatide may also be used for adults who meet the relevant eligibility criteria for treating overweight or obesity.

Results from clinical trials suggest that:

- setmelanotide may reduce weight and body mass index (BMI) in people 6 years and over with BBS
- there is more benefit for people who start setmelanotide aged between 6 and 17 years than for people who start treatment as adults
- hunger scores and quality of life are improved with setmelanotide in the short term, although hunger scores may not reliably reflect changes in hyperphagia.

The updated trial evidence suggests that setmelanotide's treatment effect on weight-related outcomes in adults may be maintained in the longer term. But this is also uncertain. Setmelanotide has not been compared with liraglutide, semaglutide or tirzepatide for treating obesity in adults with BSS.

For adults with BBS who have not started setmelanotide before age 18 years, there are uncertainties in the company's revised economic model, including:

- the average age of diagnosis in adults
- the clinical effectiveness of liraglutide, semaglutide or tirzepatide for treating overweight and obesity compared with setmelanotide
- the expected distribution of hyperphagia severity in adults before setmelanotide treatment
- the approach used for modelling changes in hyperphagia
- whether setmelanotide has added liver or kidney benefits in a mixed population of children, young people and adult above the benefits seen from reducing BMI

- how common the visual and cognitive symptoms of BBS are in people who would have treatment in the NHS
- potential uncaptured benefits.

Because of the uncertainties in the clinical evidence and economic model, it was not possible to determine the most likely cost-effectiveness estimates for setmelanotide in people starting treatment as adults. So, it should not be used for this population.

In people who start having setmelanotide aged between 6 and 17 years, and keep having it in adulthood, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, it can be used for this population.

2 Information about setmelanotide

Marketing authorisation indication

2.1 Setmelanotide (Imcivree, Rhythm Pharmaceuticals) is indicated for 'the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 2 years of age and above'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for setmelanotide.

Price

2.3 The list price of setmelanotide is £2,376.00 for a 10 mg/ml vial for injection (excluding VAT; BNF online, accessed June 2026).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes setmelanotide available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Rhythm Pharmaceuticals will be included here when guidance is published.

3 Committee discussion

For the original evaluation, the evaluation committee considered evidence submitted by Rhythm Pharmaceuticals, a critique of this submission by the external assessment group (EAG) and responses from stakeholders. For this review of NICE's highly specialised technology guidance on setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (from here, HST31), the committee considered another submission by Rhythm Pharmaceuticals, a further critique by the EAG and additional responses from stakeholders. See the committee papers for full details of the evidence.

Background

3.1 This evaluation is a review of HST31, which recommended setmelanotide as an option for treating obesity and hyperphagia in Bardet-Biedl syndrome (BBS) in people starting treatment aged between 6 and 17 years. It also recommended that these people can carry on having setmelanotide as adults until they need to stop. But the committee did not recommend setmelanotide for people starting treatment as adults. This was because the cost-effectiveness estimates in the populations including adults were substantially higher than the threshold normally considered cost effective for highly specialised technologies. That committee noted that there were greater benefits associated with setmelanotide for children and young people than for adults with BBS. It also considered that a negative recommendation in people starting treatment as adults would be proportionate to NICE's legitimate aim to recommend clinical- and cost-effective technologies.

With the aim of extending the HST31 recommendation to allow adults with

genetically confirmed BBS to start setmelanotide, the company submitted new evidence generated since HST31. The intent was to address or reduce the uncertainties identified during the original evaluation, including evidence on setmelanotide's treatment effect for people with BBS:

- on body mass index (BMI)
- on hyperphagia in adults
- in the long term
- on quality of life
- on the possible broader benefits relating to potential kidney and liver outcomes.

The committee considered the evidence on starting treatment in adults. This included whether the new evidence sufficiently addressed or reduced the uncertainties and improved the clinical- and cost effectiveness for starting treatment in adults with obesity and hyperphagia in BBS.

The condition

Details of the condition

3.2 BBS is a rare genetic disorder that results in obesity. It is caused by mutations in 1 or more of the BBS genes, of which 22 have been identified to date. These genes are involved in signalling through the melanocortin 4 receptor (MC4R) neuroendocrine system in the hypothalamus. This system regulates hunger, satiety (a feeling of fullness) and energy expenditure. Disrupted signalling through MC4R expressing neurons causes hyperphagia (characterised by a feeling similar to starvation), which can result in severe, early onset obesity. For this review, the clinical and patient experts emphasised that hunger and obesity associated with BBS differ from the general obesity that is more commonly seen in the NHS. This is because, for people with BBS, food and food noise dominates their life. BBS is likely associated with increased death rates

compared with general obesity. This is because of renal failure and early onset of comorbidities related to severe obesity in childhood, such as diabetes and cardiovascular conditions. Other symptoms include learning difficulties, visual impairment, kidney problems, extra toes or fingers, and genital or hormonal problems. The committee concluded that obesity caused by BBS is a debilitating condition associated with multiple comorbidities.

Effects on quality of life

3.3 The patient experts explained that the quality of life of people living with obesity caused by BBS can be extremely poor. They emphasised that the associated hyperphagia can be debilitating and all-consuming. Without any signal of feeling full, people with BBS can show extreme food-seeking behaviours, such as taking food out of bins or hoarding food to eat later. A patient expert explained that, before having setmelanotide, they thought about food constantly and never felt full. The resulting obesity affects mobility, sleep and concentration, and can make maintaining a healthy diet and exercise regime challenging. Learning and communication difficulties may affect quality of life, and children and young people with the condition often need support at school. Visual impairment can also be challenging, both mentally and physically, with blindness common by mid-teenage years. The committee understood that there is a significant psychological effect of living with BBS. For people with the condition, obesity can exacerbate feelings such as depression and anxiety. It is also often associated with stigma, especially considering associated learning difficulties. Carers are constantly worried about the lack of mobility and strain on the body caused by the severe obesity characteristic of BBS. One carer highlighted that hyperphagia is often misunderstood by healthcare professionals, who misinterpret the condition as general hunger. It can also be hard to access local support for related comorbidities. Siblings and the wider family are affected by the frequency of hospital visits, and the strict dietary measures needed to control hyperphagia.

During the committee meeting for this review, an adult with BBS explained that hyperphagia was exhausting and affected their confidence, mental health and quality of life. They emphasised that hunger and thinking about food were constant and did not disappear when they become an adult. A patient expert who is a carer for an adult with BBS commented that hyperphagia and obesity can be well managed when children and young people are supported and living in the family home. But more problems can arise with the transition to adulthood and the greater need for independence. It can lead to an increase in obesity. They added that, when obesity associated with BBS in a person under 18 years is well managed, they may not need semaglutide despite being eligible based on their age. But when they become an adult, their symptoms are likely to worsen, but they are no longer eligible to have semaglutide if they are not already having it. The committee concluded that BBS has a substantial impact on people with the condition, their families and carers.

Clinical management

Treatment options

3.4 Setmelanotide is available as an option for treating BBS in people starting treatment aged between 6 and 17 years through the HST31 recommendations. Since HST31, the marketing authorisation for setmelanotide has been extended from to include people 2 years and over. Use of setmelanotide in children aged 2 to 5 years is covered through NHS England specialised commissioning, so is not included here. For other populations, there are no other licensed treatments for obesity and hyperphagia caused by BBS. Also, there are no other treatments that reduce hyperphagia. Best supportive care for obesity without setmelanotide includes dietary advice to manage the hyperphagia and exercise modification.

The clinical experts explained that the standard dietary advice

interventions are rarely effective in the long term because they do not address the underlying hyperphagia. During the committee meeting for this review, an adult with BBS commented that losing weight against a backdrop of constant internal food noise is extremely difficult. The committee concluded that there is an unmet need for a new treatment for BBS, particularly in adults who have not started semaglutide before age 17 years.

Relevant comparators

3.5 The committee for HST31, agreed that bariatric surgery is rarely used in people with BBS. It noted that NICE's technology appraisal guidance on semaglutide for managing overweight and obesity had recently recommended the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide for treating general obesity in adults. The clinical experts then explained that there was limited evidence on using semaglutide in people with BBS. Semaglutide is approved for use in the NHS for a maximum of 2 years, and will likely not be used alone in people with BBS. But it may be considered in combination with other weight-loss treatments in the future. The committee for HST31 understood that, if recommended, setmelanotide would be used in addition to best supportive care with dietary and exercise interventions. So, it concluded that best supportive care without setmelanotide was the relevant comparator, and that bariatric surgery and semaglutide were not.

At the time of this review, 3 GLP-1 receptor agonists had been recommended for managing overweight and obesity in adults in NICE's technology appraisal guidance on liraglutide, NICE's technology appraisal guidance on semaglutide (from here, TA875) and NICE's technology appraisal guidance on tirzepatide. The company stated that there were no randomised controlled trials, observational studies or real-world comparative data sets on using GLP-1 receptor agonists in people with BBS that would allow a robust or meaningful direct or indirect comparison in this patient population. It also noted that, in the scope consultation for

HST31, Novo Nordisk indicated that the safety and efficacy of liraglutide for weight management had not been established for obesity secondary to endocrinological or eating disorders. So, it thought that it should be excluded as a comparator. The company added that GLP-1 receptor agonists do not address the underlying disease mechanism associated with hyperphagia in BBS, which arises from disruption of the melanocortin-4 receptor (MC4R) pathway.

The EAG highlighted comments from its clinical adviser that 1 (at Queen Elizabeth Hospital, Birmingham) of the 2 specialist centres for BBS in England had been using GLP-1 receptor agonists for treating obesity in adults with BBS for several years. This centre was understood to have treated BBS in around 50 adults among those who met the eligibility criteria for using a GLP-1 receptor agonist for BMI and weight-related comorbidities. One of the clinical experts at the meeting suggested that some adults with BBS may have a GLP-1 receptor agonist because it is the only treatment available that can help generally. Another clinical expert explained that there is limited evidence on the treatment effects of GLP-1 receptor agonists in BBS. They also noted that these treatments do not address hyperphagia nor target the underlying mechanism of BBS. They added that, if setmelanotide were available to adults, it would be used instead, including switching people on a GLP-1 receptor agonist to setmelanotide. The company noted that some people with BBS would have treatment with a GLP-1 receptor agonist for diabetes. So, in these people, setmelanotide would be used alongside a GLP-1 agonist. The committee noted that there was uncertainty about whether the BMI improvements seen in the setmelanotide trials would be replicated in a cohort already using a GLP-1 receptor agonist with some improvement in their BMI.

The committee was aware that TA875 includes a stopping rule for semaglutide, so it cannot be used for more than 2 years. The clinical

experts explained that there is large variation in the ability to access GLP-1 receptor agonists in NHS clinical practice for treating general obesity in adults. They added that this is exacerbated when considering their use in a specialist setting for BBS. So, not all adults with BBS and obesity can access treatment with a GLP-1 receptor agonist. The patient expert explained that their specialist centre had referred them to primary care for treatment with a GLP-1 receptor agonist. But their primary care practitioner was not willing to prescribe one because their obesity is caused by BBS. The committee understood that not everyone with BBS who is eligible for a GLP-1 receptor agonist for obesity can access these treatments. It also understood that this may be partly an implementation issue because of the phased roll out of tirzepatide. It also noted that the evidence on GLP-1 receptor agonists for treating obesity in people with BBS is limited, but data may be available from one of the BBS specialist centres.

The committee decided that it was reasonable to include GLP-1 receptor agonists alongside best supportive care as comparators for this review. This was because GLP-1 receptor agonists are now established treatments for obesity generally. Although it understood that they are being used according to their eligibility criteria by some healthcare professionals in the NHS to treat obesity in adults with BBS. Also, if setmelanotide were to be recommended for adults, the committee heard that people already having a GLP-1 receptor agonist would likely be switched to setmelanotide. So, the committee concluded that both GLP-1 receptor agonists (liraglutide, semaglutide and tirzepatide) and best supportive care were relevant comparators and should be included in the economic model for adults. It also concluded that not all adults with BBS can access them for obesity due to the eligibility criteria currently in place and that this should be reflected in the modelling.

Decision problem

Company's population in HST31

3.6 The committee for HST31 initially concluded that the whole population in the marketing authorisation should be considered for decision making (more detailed consideration of the company's original population for the decision problem is included in the guidance). But, during the evaluation, the company requested that the committee consider a recommendation in people who start setmelanotide as children. This was because there was likely a larger treatment effect in children and young people than in adults. The committee then agreed that a subgroup effect in children and young people was biologically and clinically plausible. The committee preferred the mixed population but considered the subgroup analyses in which everyone entered the model as children. So, it recommended starting setmelanotide in this subgroup (see section 3.1).

Company's population for the review

3.7 The population in the NICE scope for this review was adults with obesity and hyperphagia in BBS. The company limited its population in the decision problem to adults with BBS and a BMI of 30 kg/m^2 or more. It also included a co-base case for the economic mode. This included everyone with BBS 6 years and over. In the trial, obesity criteria were defined as a BMI above the 97th percentile in people aged 6 to 15 years or a BMI of 30 kg/m² or more in people 16 years and over. The company suggested that a consideration of this co-base case in the whole population provided context to the adult population. It explained that this was because understanding of BBS had evolved in people of all ages. Also, new evidence to address the uncertainties identified in HST31 included evidence for the whole population. The committee agreed but noted that patient-reported evidence on hyperphagia severity was only in adults. The company added that its whole population co-base case avoided inequity concerns (see section 3.33). This was because starting setmelanotide later in life does not capture the full potential lifetime

benefits of treatment through undiscounted quality-adjusted life year (QALY) gains. The committee recalled that, in HST31, setmelanotide was not cost effective in the mixed population of children and adults. It also recalled the reasons that HST31 recommended starting setmelanotide in people aged 6 to 17 years (see section 3.1 and HST31).

The EAG thought that the company's base-case population was appropriate. But it thought that the co-base case was not directly relevant to the decision problem for the review. So, the EAG only included adults in its base case. But it explored analyses that had been applied to the company's co-base for the whole population. It also noted a distinction between:

- adults who did not have setmelanotide as a child but who would be eligible for setmelanotide if it were recommended for adults who have not had it before age 18 years
- adults who have a BBS diagnosis as an adult in the future, and
- adults whose BBS was diagnosed when they were under 18 years but whose hyperphagia and obesity did not meet the criteria for setmelanotide until they were adults.

It explored the impact of the model starting age for adults (see section 3.15). It also suggested that there may be inequity issue for people with BBS who were already 18 years or over before HST31 was published, so had not been able to start treatment during childhood (see section 3.33).

The committee was aware that starting setmelanotide in people aged 6 to 17 years did not reflect with BBS in the NHS for whom it is licensed for. But, because the recommendation was already made for the subgroup of children and young people, the scope for this review was to:

- consider new evidence on starting setmelanotide for BBS in adults and
- determine whether setmelanotide is cost effective for people starting treatment as adults because they do not currently have access to it.

The committee concluded that adults with BBS and a BMI of 30 kg/m^2 or more was the population that should be considered for decision making in this review. It also decided that the decision problem should include consideration of GLP-1 receptor agonists as well as best supportive care as relevant comparators for some adults (see section 3.5).

Clinical effectiveness

Data sources

3.8 The main clinical trial evidence for setmelanotide came from a phase 3 trial, RM-493-023, referred to as the 'pivotal trial' in this guidance. It has enrolled 44 people with BBS. The trial had 2 stages:

- Stage 1: this was a 14-week double-blind randomised placebo-controlled stage that enrolled people 6 years and over with a BMI of 30 kg/m^2 or over (or the 97th percentile or more in people under 16 years). There were 22 people randomised to placebo and 22 people randomised to setmelanotide.
- Stage 2: this was an open-label treatment period of up to 52 weeks. Everyone in this stage of the trial (including people randomised to placebo in stage 1) had setmelanotide. Efficacy outcomes were assessed at 52 weeks of active treatment for each group (after 52 weeks for people randomised to setmelanotide and after 66 weeks for people randomised to placebo and who started setmelanotide after week 14).

People having setmelanotide in the trial had a maximum of 3 mg per day after dose escalation. The trial enrolled 2 separate cohorts:

- The pivotal cohort included the first 32 people enrolled in the study and informed the analyses at 52 weeks.
- The supplemental cohort included a further 12 people, who could enter an open-label study from week 24, so only 14-week data was used for analyses.

The company also provided evidence for setmelanotide from a phase 3 open-label extension study, RM-493-022. This is an ongoing long-term follow-up study of RM-493-023 and RM-493-014. RM-493-014 was a phase 2 single-arm open-label basket trial that enrolled 10 people with BBS as well as people with other rare genetic disorders of obesity. People in RM-493-022 will have a further 2 years of setmelanotide at the same dose as used in the index trials. For HST31, results were available up to week 89. For this review, the company provided longer-term data in a small number of people having setmelanotide for up to 5 years (see section 3.11). The committee concluded that RM-493-023 and RM-493-022 were the most appropriate data sources to inform the clinical effectiveness of setmelanotide.

Assessment of the trials and outcomes in HST31

3.9 More detailed consideration of the trial outcomes and related assessments is included in HST31. This includes the following conclusions by the HST31 committee on:

- Generalisability: RM-493-023 and RM-403-022 were likely generalisable to the BBS population in clinical practice.
- Obesity-related outcomes: Setmelanotide likely improves obesity-related outcomes in the short term, but the results were associated with uncertainty.
- Other key clinical outcomes: Setmelanotide likely improves hunger and metabolic outcomes in, and the quality of life of people with BBS in the short term, but the results were uncertain.

- Potential bias in RM-493-023: There was potential bias from a lack of randomised controlled data at week 52, so results should be adjusted to account for a possible placebo effect.
- Stopping treatment: In clinical practice, response to setmelanotide would be assessed at 14 weeks by a multidisciplinary team.

Long-term treatment effects

3.10 The committee for HST31 noted that evidence from the extension study RM-493-022 suggested that changes in weight and BMI were maintained from the pivotal study baseline (exact results are confidential so cannot be reported here). But the EAG highlighted that the results of the extension study were associated with considerable uncertainty. There were very few people with data available at the 36-week follow up. This was especially so for weight loss when the company excluded children and young people because they were still growing. The committee also noted that hunger and quality of life had not been measured in the extension study. So, there were no results past 52 weeks of setmelanotide use for these outcomes.

New clinical trial evidence from the company for this review

3.11 For this review, the company provided updated long-term extension data on setmelanotide from RM-493-022. This was for the obesity-related outcomes of change in body weight (Yanovski et al. 2023) and change in BMI (Argente et al. 2026). The evidence showed that:

- in adults, there was:
  - A 15.3% (standard deviation [SD] 11.5) mean reduction from baseline in body weight at 3 years (N=10)
  - An 8.2% (SD 31.3) mean reduction from baseline in BMI at 4 years (N=3)
- in the whole population, there was an 8.8% (SD 22.0) mean reduction from baseline in BMI at 5 years (N=4).

The committee noted that the extension study suggested that changes in weight and BMI continued to be maintained in the extended follow up. It noted that weight loss (the primary endpoint of RM-493-023) was only measured up to 3 years. The EAG highlighted that the weight and BMI results had a very small sample size so were uncertain. As in HST31, results from RM 493-022 trial did not directly inform the company's model. But year 4 and 5 follow-up data was used to support the company's assumptions for the longer-term weight trajectories of people having setmelanotide. The committee concluded that the new trial evidence suggested that setmelanotide's treatment effect on weight-related outcomes may be maintained in the longer term, but that this was uncertain.

The committee recalled its discussions on relevant comparators (see section 3.5). So, it requested that the company provide an indirect treatment comparison to compare the treatment effect of setmelanotide with GLP-1 receptor agonists plus best supportive care on weight-related outcomes in adults with BBS (see section 3.29). The committee also requested that the company explore the proportion of adults with BBS in NHS practice who would be expected to have access to GLP-1 receptor agonists for overweight or obesity. This would inform a basket comparator that includes GLP-1 receptor agonists plus best supportive care, which reflects current clinical practice.

New evidence from other sources

3.12 For this review, the company compared 52-week data from RM-493-023 with an external matched control group from the international Clinical Registry Investigating BBS (CRIBBS). This was because of the lack of a placebo-controlled comparison beyond 14 weeks from the trials. Fifty-eight people from the registry (30 adults and 28 children and young people) were matched with 29 people who completed 52 weeks of setmelanotide in RM-493-023 (15 adults and 14 children and young people). The results of this comparison were used to inform the

company's updated BMI class shifts for adults in the model (see section 3.18). The EAG thought that the matched analysis using propensity scores was a reasonable approach to take for the simulated comparison with CRIBBS in the absence of randomised evidence. But the EAG had concerns with the validity of the indirect comparison because of:

- limitations with matching
- differences in best supportive care across individuals and settings
- generalisability to a UK context.

It noted that there was matching for age, baseline BMI, sex, country, type 2 diabetes, ethnicity, developmental delay, and previous weight-loss interventions. But psychological factors (anxiety, depression, trauma, and childhood experience) and cognitive phenotype were not accounted for. It also noted that the indirect comparison did not adjust for artefacts from inclusion in a clinical trial including any placebo effect (see section 3.18).

New patient-reported evidence on hyperphagia severity is described further in section 3.17. This substudy of the UK hyperphagia severity in BBS (HSinBBS) study reported by Mossman et al. (2026) collected evidence from adults with BBS and informed the baselined hyperphagia distributions in the model. There was no data past 52 weeks for the effects of setmelanotide on hunger and quality-of-life outcomes from the company's trials. So, the company presented results from other sources, including 2 single-arm prospective observational studies of setmelanotide in Europe. In France, a study of adults by Mifsud et al. (2025) showed that, in people starting setmelanotide at entry to the study, body weight decreased by an average of 14% at 6 months and 20% at 12 months. But, for people who had had setmelanotide before, there was no further weight loss or weight gain. In Germany, a study of adults and children by Hühne et al. (2026) reported a statistically significant absolute weight loss of 8.2 kg (95% confidence interval 6.46

to 9.97) in adults at 6 months. The EAG noted this data was limited by comparing outcomes with baseline values rather than with a control arm.

The 2 observational studies also provided evidence on hyperphagia improvement, hunger and eating behaviour. The EAG used this evidence to inform its preferred modelling of hyperphagia transitions (see section 3.17). The company also used data from Hühne et al. in children, young people and adults to inform its assumptions about potential treatment effects on setmelanotide on liver (metabolic dysfunction-associated steatohepatitis [MASH]) or kidney disease (see section 3.19 and section 3.20). The committee concluded that new evidence from real-world cohorts helped to reduce some uncertainty when there were gaps in the company's trial evidence. But it also noted the uncertainty in the evidence, including:

- that some evidence was for a mixed population of children, young people and adults
- uncertainty in the validity and UK generalisability of the indirect comparison with CRIBBS registry data used to model treatment effect on BMI
- that other real-world cohorts had a single arm before-after study design and evidence with limited follow up.

Economic model

Company's modelling approach

3.13 The company developed a lifetime model based on UK life tables to estimate the cost effectiveness of setmelanotide. Health states in the model included 7 BMI-Z classes (0 to 1, over 1 to 2, 2 to 4 in increments of 0.5 and over 4) for children and young people, 7 BMI classes (25 to 50 in increments of 5 and over 50) for adults and death. People with BBS entered the model having setmelanotide plus best supportive care or best

supportive care alone. After 14 weeks, they transitioned between BMI class levels depending on the clinical response to setmelanotide. The company assumed a BMI drop for people whose condition responded to setmelanotide. People whose condition did not respond changed to best supportive care alone at 14 weeks and immediately returned to their baseline BMI class. At 18 years, BMI-Z scores were mapped to the respective BMI score. People could transition to death from any BMI or BMI-Z health state. The EAG noted that this was the same structure as used as in HST31. It thought that the company's model structure for this review was appropriate to capture the lifetime costs and health-related quality of life (HRQoL) of setmelanotide.

During the committee meeting for this review, the committee recalled its discussion on relevant comparators and use of GLP-1 receptor agonists for obesity in some adults with BBS (see section 3.5). It understood that not all adults with BBS and obesity can access them. So, it thought that a basket approach, in which evidence on GLP-1 receptor agonist effectiveness and costs is included for a percentage of people in the model, reflecting the likely proportion of adult with BBS who can access them for overweight and obesity in the NHS. It was aware that GLP-1 receptor agonists are not expected to have an impact on hyperphagia symptoms. It noted that the company's model structure, which modelled BMI impact separately from hyperphagia effects, would allow for the impact of GLP-1 receptor agonists to be applied to BMI only. The committee discussed potential sources of evidence that could be incorporated in the model (see section 3.29 for suggested analyses). It concluded that the company's model structure based on BMI classes was acceptable for decision making. But it added that it would like the company to revise the model to compare setmelanotide with a basket comparator that includes GLP-1 receptor agonists which reflects the proportion of adults with BBS who have access to them in the NHS.

Population in the model

3.14 Discussion of the company's population in the original model is included in HST31. The committee recalled that the committee for HST31 concluded that it was appropriate to use the scenario that best represented current clinical practice in decision making. But it also noted the uncertainty in the distribution of children and young people, and adults. So, it preferred the mixed population but also considered subgroup analyses in which everyone entered the model as children. For this review, the company's base-case population was adults with BBS, severe or moderate hyperphagia, and obesity who start treatment aged 18 years or over. It also presented a co-base case for the whole population, that is people with BBS, severe or moderate hyperphagia and obesity aged 6 years or over. The company retained the proportion of children, young people and adult initiators in the whole population that were assumed in HST31. It considers these proportions confidential, so they cannot be reported. The committee recalled its discussion of the population for the decision problem and its view that this should be adults with BBS (see section 3.7). It also recalled its decision that GLP-1 receptor agonists were a relevant comparator for some adults in the model. The committee concluded that it was appropriate to use the population that best represented the NICE scope and the current unmet need. So, it preferred the company's base-case population in adults for decision making.

Model starting age

3.15 The NHS commissioning expert described how BBS clinics have been working to reduce the age at which BBS is diagnosed. This has been successful and means that most people are diagnosed in late childhood or their early teenage years. The company assumed that the mean age of adults starting the model was 20 years. It suggested that, if setmelanotide is made available to adults and once existing adults with BBS have had treatment, any new adult initiators would start treatment near the beginning of adulthood. The committee acknowledged that, if

recommended in adults, setmelanotide could be started at the start of adulthood. But it thought that the model starting age should be based on the age of adults in the NHS today whose BBS could be treated with setmelanotide (the prevalent cohort). It heard that people could be newly diagnosed with BBS in adulthood. So, the starting age in the model was likely to be older than 20 years. The EAG preferred to use the mean age of adults in RM-493-023 at the start of the model, which was 28.5 years. This was similar to the mean age in Hühne et al. (2026) used by the company for the liver and kidney effects of setmelanotide. The EAG explained that the mean age of adults in the UK BBS registry was 35 years. This represented the age of adults currently diagnosed with BBS in the UK, irrespective of their age at diagnosis. The committee decided that the EAG's preferred age of 28.5 years was reasonable. This was most likely to reflect the current population of adult with BBS who might start setmelanotide. It thought that this took account of both that people with BBS are starting to be diagnosed at a younger age than in the past and that some people will still be newly diagnosed as adults. So, it concluded that 28.5 years was the most appropriate model starting age.

Baseline hyperphagia status for adults

3.16 Discussion of the company's original approach for hyperphagia severity at baseline is included in HST31. The committee recalled that, the committee for HST31, concluded that the distribution of hyperphagia severity levels at baseline was unknown. Also, although the assumption that 75% of people had severe and 25% had moderate hyperphagia was preferred to illustrate the BBS population entering the model, this was highly uncertain. For this review, the company presented new evidence from the UK HSinBBS study. In a subset of this study, described by Mossman et al. (2026), 39 adults had hyperphagia assessed by questionnaire. Then 13 of the 39 had a semistructured interview. The company used the severity distribution derived from the 13 interviews in the model. The EAG noted that there was a large difference in hyperphagia severity results between the questionnaires (8% severe, 51%

moderate and 41% mild) and interviews (69% severe, 31% moderate and 0 mild). They added that the cost-effectiveness results were highly sensitive to this assumption.

The company explained that, for the questionnaires, people completed these themselves without input from an interviewer or clinical expert. People having interviews were self-selected. They were done by an independent interviewer and then clinical expert input was incorporated based on the transcript. The company suggested that people with BBS tend to under-report hyperphagia. So, the interviews were important to help people fully recognise their symptoms. A clinical expert noted that issues such as the disability paradox (in which many disabled people report a high quality of life), stigma, shame and problems with self-reporting may be magnified in BBS. The EAG agreed that the interviews offered an opportunity to probe, clarify and contextualise responses. So, they may also have had greater construct validity for informing the classification of hyperphagia severity in this population. The EAG also highlighted during the meeting that interviews may be subject to selection bias or influence of interviewers, but it could not assess these risks because of the lack of reporting. So, the EAG considered that the interview findings should supplement rather than replace those from the questionnaires. The EAG used the interview results in its base case. But suggested that it would be reasonable to take a weighted approach to incorporating the questionnaire data as well. The company explained that 15 out of 39 people who completed the questionnaires were randomly selected, and 13 interviews were done. The EAG noted that, among the 13 people with BBS interviewed, 8 had moderate and 5 mild hyperphagia, none had severe hyperphagia. It thought that it was unclear how the 13 people had been sampled. The committee decided that, by relying on the interview data only, the company was not using all of the data in the study. It concluded that the baseline distribution of hyperphagia among adults remained unclear and no conclusion could be made given the

information available. It requested that the company provide transparent reporting of the study methods for both the questionnaire and the interviews. This should include, but not be limited to:

- how the people were selected
- how potential risks of bias were assessed, including sampling and selection bias, data collection, interviewer influence, the conduct of interviews, recall, and interpretation and analysis of the data.

Hyperphagia transitions

3.17 More details of the company's original approach for modelling treatment effect on hyperphagia is included in HST31. In line with HST31, the company for this review assumed that setmelanotide reduces hyperphagia by people moving between severity states in the model. Because there was no direct data to inform this, the company used changes in BMI-Z from RM-493-023 to inform the transitions between hyperphagia states. The EAG noted that there was very little evidence to inform the proportions moving from the severe or moderate hyperphagia states, and so there remains uncertainty in this:

- For transition from severe hyperphagia: the company's assumption was in line with the committee's preference from HST31. For people starting with severe hyperphagia, the company assumed that 17% of people whose BBS responded move to moderate hyperphagia and 83% move to mild hyperphagia. In the absence of further evidence, the EAG considered it appropriate to use the same transition proportions as preferred by the committee for HST31 for those starting in the severe hyperphagia state.
- For transition from moderate hyperphagia: the company updated its approach from HST31, in which 100% of people were assumed to move to mild hyperphagia. Based on opinion from a clinical expert, it assumed that 70% of people with moderate hyperphagia at baseline whose BBS responded would move to mild hyperphagia and 30% would move to having no hyperphagia. The EAG was concerned about

the robustness of this estimate and sought additional clinical advice and evidence. It thought that it was reasonable that some people would move to having no hyperphagia. But, based on the limited evidence from Mifsud et al. (2025) and Hühne et al. (2026; see section 3.12), the EAG assumed that 80% of people with moderate hyperphagia at baseline whose BBS responded would move to mild hyperphagia and 20% would move to having no hyperphagia. It also noted uncertainty around these estimates.

The committee decided that it could not make a decision about the hyperphagia transitions because of the uncertainty in the baseline hyperphagia severity estimates and request for more information (see section 3.16). So, it concluded that it was unable to make a conclusion for hyperphagia transitions in the model.

Modelling treatment effect on BMI

3.18 As done in HST31, the company used data from RM-493-023 to inform the following model inputs in this review:

- the distribution of people in each of the 7 BMI score (adult) and BMI-Z score (children and young people) health states at baseline
- the response rates for setmelanotide at 52 weeks
- the size of the treatment effect on BMI, based on BMI or BMI-Z score reductions, translated to shifts in modelled BMI class levels. The company updated its approach for calculating these BMI class shift reductions for the review.

For adults, the company adjusted the mean BMI change (decrease) for setmelanotide at 52 weeks in the trial by the change in BMI (increase) seen in the external matched control group from the UK CRIBBS registry (see section 3.12). This gave a BMI class shift reduction of 1.37 for adults whose BBS had a response to treatment. The company justified its approach by suggesting that any trial placebo effect is not

long term, and people on best supportive care would revert to their original BMI. The EAG noted that the company's approach relied on an indirect comparison, which had some issues (see section 3.12). These included that best supportive care varied at the patient level and people from the UK were excluded. It suggested that the company's approach did not adjust for artefacts from inclusion in a clinical trial, such as regression-to-the mean, as seen in setmelanotide data. As discussed in HST31, the EAG noted that there was evidence of an early drop in BMI or BMI-Z by week 4 of the trial, before stabilisation in the placebo arm up to 14 weeks. After this, people in the placebo arm switched to setmelanotide and their BMI fell to the same levels as those in people in the setmelanotide arm. The HST31 committee's preference in was to use the mean trial BMI adjusted for a placebo effect. So, the EAG preferred to adjust the mean BMI change for setmelanotide at 52 weeks for the trial placebo effect seen at 14 weeks. This gave a smaller BMI class shift reduction of 1.23 for adults whose BBS had responded.

The EAG explained that modelling treatment effect on BMI-Z in children and young people was only relevant when modelling whole population. It noted that the company updated its approach for children and young people for this review. This was to use mean BMI change for setmelanotide at 52 weeks without adjustment. This gave in a BMI-Z class shift reduction of 1.74 for children and young people whose BBS had responded. The EAG preferred to adjust the mean BMI-Z change for setmelanotide at 52 weeks for the trial placebo effect at 14 weeks. This was the approach the HST31 committee preferred and it was consistent with the EAG's approach in adults in this review. This gave in a smaller BMI-Z class shift reduction of 1.56 for children and young people whose BBS responded. The committee decided that the company's approach for modelling treatment effect on BMI overestimated the modelled treatment effect on BMI in children, young

people and adults. It concluded that it preferred the EAG's approach for both, which adjusted for the placebo effect at 14 weeks seen in the trial.

Additional treatment effect on MASH

3.19 The committee noted that the company's model for this review was consistent with that for HST31. The prevalence of fat-associated liver disease (metabolic dysfunction-associated steatotic liver disease [MASLD] and MASH) as a comorbidity was modelled based on BMI or BMI-Z category and age for both setmelanotide and best supportive care. This was associated with additional costs and utility decrements. People can then have a lower prevalence of MASLD and MASH from a reduction BMI or BMI-Z. For this review, the company provided new observational evidence in children, young people and adults from Hühne et al. (2026; see section 3.12). This was a single-arm prospective observational cohort study assessing the differences in fat-associated liver disease before and after treatment with setmelanotide. This suggested that MASLD had resolved for 54% of people who had treatment with setmelanotide and had stabilised at mild MASH (grade S1 hepatic steatosis) for 27% people. So, the company assumed an 81% reduction factor for MASH because of setmelanotide in the model. The EAG explained that the Hühne et al. study was single arm in design and the company did not adjust for change in BMI with setmelanotide in its statistical analyses. So, it was not known whether the effect of setmelanotide on MASH was additional to that seen with an improvement in BMI. It also noted the uncertainties that may be associated with the evidence because the study numbers were small and there was not control group.

The EAG's clinical advisers did not think an effect of setmelanotide on MASH additional to that caused by a change in body weight or BMI was biologically plausible. The EAG preferred to remove the MASH reduction factor for setmelanotide from the model. It also explored the impact of applying a lower reduction factor (54%). A clinical expert at the meeting indicated that there is early evidence that setmelanotide has an effect on

liver fat which is greater than might be expected by weight loss alone. They suggested that this may be mediated effects on peripheral storage of triglycerides. Considering the uncertainty in the evidence and limitations in company's analysis, the committee decided that it had not seen robust evidence that setmelanotide had an effect on MASH that was additional to that achieved through a change in BMI. It thought that setmelanotide may have benefits for MASH, but these may have been captured in the model through the BMI analysis. It concluded that it was reasonable that the model included costs and disutilities of MASLD and MASH as a comorbidity for both arms of the model. But it preferred the EAG's approach that removed setmelanotide's additional effect on MASH beyond its effect on BMI.

Additional treatment effect on kidney disease

3.20 The committee noted that, for this review, the company's updated model added a prevalence of kidney disease for both setmelanotide and best supportive care. Five kidney function categories, defined by estimated glomerular filtration rate (eGFR), were modelled. These were associated with different additional costs and utility decrements. The company noted that the costs and utility decrements applied for kidney disease in the model were based on the general population, not on people with BBS, so were underestimates. The company's approach assumed that setmelanotide would improve kidney function based on results of Hühne et al. (2026). The EAG explained that there were multiple methods presented in Hühne et al. to calculate eGFR. These were used to categorise the kidney function at baseline and measure a potential treatment effect. The company's preferred approach was suitable for measuring eGFR in people under 25 years (creatinine; Chronic Kidney Disease in Children [CKiD] score). It produced the largest treatment effect of setmelanotide on kidney function. The EAG noted that the company applied this treatment effect of setmelanotide to the whole population (all ages) in the model. The EAG thought that an alternative method to calculate eGFR that was suitable for adults and people under 25 years

(creatinine plus cystatin C; Chronic Kidney Disease Epidemiology Collaboration; CKiD) and its associated treatment effect would be more appropriate. The EAGs clinical advisers did not think setmelanotide would have an independent effect on kidney disease beyond that caused by a change in BMI.

A clinical expert at the meeting suggested that, if setmelanotide has an effect on kidney disease that is greater than might be expect by weight loss alone, this might be mediated by changes in kidney blow flow. The EAG noted that the analysis of kidney function in Hühne et al. did not adjust for change in BMI in its statistical analyses. Because of it this, it preferred to remove this from the model to avoid double counting. The committee recalled its discussion on the limitations of Hühne et al. and the uncertainties in it results. It decided that it had not seen robust evidence that setmelanotide had an effect on kidney disease additional to that seen through a change in BMI. It concluded that it preferred the EAG's approach that removed baseline kidney disease, and costs and disutilities associated with change in kidney function from the model.

Treatment stopping

3.21 The committee noted that the company's model was consistent with that in HST31, in that an annual stopping rate of 1% was assumed for people whose BBS responded to setmelanotide. It suggested that this was consistent with the low stopping rates seen in real-world studies of setmelanotide. The EAG explained that follow-up data from company's open-label extension study included stopping rates of 0.6% because of adverse events and 4.5% when voluntary withdrawals were included. So, it suggested that this provided a plausible range for modelling treatment stopping. The EAG did a meta-analysis of evidence from the trials and real-world cohorts. This suggested a stopping rate of 3.42%, which the EAG preferred for its base case. The EAG noted that there was some uncertainty because the real-world evidence included people whose BBS had not responded to setmelanotide. Also, 1 cohort was in BBS and

related genetic conditions. But it thought that 3.42% was within the plausible range and it explored other values in scenarios. The EAG added that the stopping rate modelled had a small impact on the incremental cost-effectiveness ratio (ICER) in the adult population. But it had a large ICER impact in the whole population (company co-base case) because it reduced the QALY weight that could be applied (see section 3.25). The committee acknowledged the compelling testimony of the patient expert who described having setmelanotide in a clinical trial. The patient expert explained that it was the first and only time they had not felt exhausted by the constant need to eat. They had eaten smaller portion sizes, and felt happier and more confident. So, the committee thought that people would generally be very reluctant to stop treatment with setmelanotide. It decided that the 1% stopping rate assumed by the company was within the plausible range. So, it concluded that a stopping rate of 1% should be assumed for people whose BBS responded to setmelanotide in the model.

Utility values

Source of obesity-related utility values

3.22 The company updated its evidence source for the impact of BMI on utilities for this review. It used EQ-5D-3L data measured on people in the UK having a weight-loss intervention to get utilities by BMI or BMI-Z category (Breeze et al. 2022). It suggested that its updated approach overcame limitations with the approach taken in HST31, in which:

- PedsQL scores in children from Riazi et al. (2010) were mapped to EQ-5D by BMI-Z
- SF-12 data on US Medical Expenditure Panel Survey was mapped to EQ-5D by age and BMI in adults.

The EAG agreed with the company that using directly observed preference-based utilities is preferable to mapping from PedsQL or SF-12 to EQ-5D in an appropriate population. It noted that Breeze et al.

included adults with mean age of 53 years who were having a behavioural group-based weight-loss intervention. The EAG noted that the population in Breeze et al. is, on average, older than that in the UK BBS registry and does not include BBS. But it thought that it was the most appropriate available source of obesity-related utility values for adults with BBS. So, the Breeze et al. values were applied in the EAG's base case. But, when considering the whole population, the EAG thought that Breeze et al. was not a suitable source of utility values for children and young people. For them, it preferred to retain the PedsQL scores from Riazi et al. and mapped to EQ-5D by BMI-Z, as done in HST31 in the company's co-base case. The committee concluded that the source of utility values used for children and young people was relevant for the whole population only. It preferred the adult population for decision making. It also concluded that it agreed with the company and EAG on the updated approach for incorporating the impact of obesity-related utility values for adults.

Non-obesity symptoms disutility

3.23 For this review, the company updated its approach for incorporating the impact of non-obesity-related BBS symptoms. This was based on the prevalence of visual and cognitive impairments of BBS in RM-493-023. The company attributed disutilities to these from a UK catalogue of the EQ-5D-3L utility population. It also presented a scenario using the BBS utility multiplier of 0.87, which was derived from mapped PedsQL data in RM-493-023, as used in HST31. (More detailed discussion of the previous approach is included in HST31.) The EAG agreed that it was appropriate to capture the impact of non-obesity-related BBS symptoms on HRQoL in the model. It also thought that the company's updated approach was more appropriate than the method used in HST31. So, it applied the updated approach to the EAG's base case. The EAG noted that it was uncertain whether the prevalence of visual and cognitive impairments in the trial reflected those seen in NHS practice. It suggested that real-world data could be presented to validate the trial prevalence estimates. The

committee concluded that it agreed with the company and EAG agreed on the updated approach for incorporating the impact of non-obesity-related BBS symptoms in the model. It also concluded that there was uncertainty in the underlying prevalence estimates of visual and cognitive impairments of BBS.

Carer disutility

3.24 The clinical and patient experts contributing to the review explained that BBS places a substantial burden on carers (see section 3.3). As in HST31, the company included a utility decrement to reflect this. A patient expert who was a carer explained that most people with BBS continue living in the family home as they become adults. They noted that there can be increasing difficulty and conflict as people with BBS move from childhood to adulthood with the greater need and expectation of independence and autonomy. The committee noted that the company assumed an average of 1 carer per adult with BBS. The committee concluded in HST31 that the assumption of 1 carer per adult with BBS in the model was reasonable for decision making. Unlike in HST31, the company assumed for this review that the change in average number of caregivers (from 1.5 for children and young people) is not sudden at the point a young person with BBS reaches 18 year, but instead taper from 1.5 to 1 linearly between the ages of 18 years and 25 years. The company also provided a scenario with no tapering. The EAG noted that it assumed a higher mean age for adults entering the model than the company did (see section 3.15). So, although the EAG applied the company's taper in its base case, it had no effect. The committee recalled that, like the EAG, it preferred 28.5 years as the model starting age. So, it concluded that the company's taper had no effect in its preferred base case in adults.

QALY weighting criteria

3.25 The committee understood that NICE's technology appraisal and highly specialised technologies guidance manual specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised

technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs.

The committee for HST31 noted that some of the company's and EAG's analyses showed QALY gains within this range. The committee recalled the multiple sources of uncertainty, as described in HST31. So, it concluded that there was too much uncertainty around the exact QALY gains to consider this 'compelling' and to apply 100% of a QALY weight. The committee thought that most of the QALY weighting should be applied, but wanted to account for some of the uncertainty. So, it concluded that applying a deliberative 90% of QALY weighting was appropriate for its decision making.

For this review, the committee noted that, in both the company's and EAG's preferred base case in adults, there were fewer than 10 QALYs gained. The EAG explained that, unlike the approach taken in the evaluation for HST31, the company applied a QALY weight in each iteration of the probabilistic analysis. This meant that multiple QALY weights were averaged to get a mean weighted incremental QALYs. The company's approach gave an average QALY weight of 1.05 for the adult population. The EAG thought that the company's approach was atypical because a single QALY weight is usually applied outside of the probabilistic analysis. This was the EAG's preferred method and it gave a single QALY weight of 1, so no QALY weight was applied for the adult population. The company suggested that its approach was suitable for capturing uncertainty in the QALY weight. It noted that it had been

accepted by committees in the past, including in NICE's highly specialised technologies guidance on pegzilarginase for treating arginase-1 deficiency in people 2 years and over. The EAG noted that the NICE manual does not specify a preferred method for applying a QALY weighting in the probabilistic analysis. The EAG explained that the HST35 committee wanted to capture the high uncertainty around the QALY weight, which ranged from 1 to 3. So, it was not likely affected by being truncated at 1. The EAG also noted that, in the current evaluation, the QALY weight the company uses was pushed upwards in the adult population in the probabilistic analyses. This was because the QALY weight cannot be below 1. The committee understood that the company and EAG had different approaches to applying QALY weighting in the probabilistic analysis, and this affected the results. It concluded that, because of the uncertainties identified in the evidence and requested analyses (see section 3.16 and section 3.29), it was unable to make a conclusion on QALY weighting.

Uncertainty in the review

3.26 The committee welcomed the additional and new evidence submitted by the company to address the uncertainties identified during HST31. But it noted that substantial uncertainties remained, including some new sources of uncertainty. Several of these were key drivers of the cost-effectiveness results, specifically:

- the long-term treatment effects of setmelanotide in adults (see section 3.11)
- the baseline hyperphagia severity distributions in adults and transitions (see section 3.16 and section 3.17)
- setmelanotide's treatment effect on BMI in adults (see section 3.18)
- the treatment effect of GLP-1 receptor agonists on BMI in some adults with BBS, and its treatment effect relative to setmelanotide (see section 3.5)

- whether setmelanotide had a treatment effect on liver or kidney disease beyond its effect on BMI in adults (see section 3.19 and section 3.20)
- the stopping rate for setmelanotide (see section 3.21)
- the prevalence of non-obesity-related comorbidities in adults who would have treatment with setmelanotide in the NHS (see section 3.23)
- how QALY weight, if it applies, should be used in the probabilistic analysis (see sections 3.25).

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates for the review

3.27 The company's base-case results in adults showed that setmelanotide was associated with an ICER of substantially above £100,000 per QALY gained compared with best supportive care. This was including when a QALY weight of 1.05 was applied through the company's approach in its probabilistic analyses and using the EAG's preferred approach in which the QALY weight was 1 (see section 3.25). In the EAG's base case, the ICER for setmelanotide compared with best supportive care was also substantially above £100,000 per QALY gained (irrespective of the approach to calculating and applying a QALY weight). All ICERs are confidential because they include the confidential discount for setmelanotide available to the NHS.

The company's co-base-case results in the whole population gave an ICER of below £100,000 per QALY gained for setmelanotide compared with best supportive care. This was using both the company's or EAG's method for calculating and applying a QALY weight in the probabilistic analyses. But, when applying the EAG's preferred assumptions to the company's co-base-case results for whole population, the ICER for setmelanotide compared with best supportive care was substantially above £100,000 per QALY gained (irrespective of the approach to calculating and applying a QALY weight).

Preferred assumptions for the review

3.28 The committee decided that the adult population should be used for decision making for this review. Considering the company's and EAG's analyses, the committee's preferred assumptions for the adult population included:

- long-term effects
- that the relevant comparators were best supportive care and GLP-1 receptor agonists
- using a model starting age of 28.5 years
- using the EAG's preferred treatment effect on BMI score for adults, which adjusted for the placebo effect seen in the trial
- removing the company's additional treatment effects on MASH and kidney disease form the model
- using the company's preferred a 1% annual stopping rate
- using obesity-related utility values for BMI for class health states from the study by the Breeze et al. (2022), which the company and EAG preferred
- using the prevalence of visual and cognitive impairments in the trial, then applying attributed disutilities to these from a UK catalogue of EQ-5D-3l utility population to incorporate the impact of non-obesity-related BBS symptoms
- assuming 1 carer per adult with BBS.

The committee noted it was not able to state a preference for the baseline hyperphagia severity distribution (section 3.16) or hyperphagia transitions (section 3.17). It also thought that the model did not consider all relevant comparators for adults so requested additional evidence and analyses (see section 3.29).

Requested evidence and analyses for the review

3.29 The committee requested that the company provide an indirect treatment comparison between setmelanotide and GLP-1 receptor agonists plus best supportive care on weight-related outcomes in adults with BBS. It also asked the company to explore the proportion of adults with BBS in NHS practice who would be expected to have access to GLP-1 receptor agonists for overweight or obesity (see section 3.11).

The committee requested that the company revise its model to incorporate evidence on the potential treatment effect GLP-1 receptor agonists on obesity in adults with BBS relative to setmelanotide. It noted that this should be applied through the modelling of BMI in adults. The committee acknowledged that not all adults with BBS can access GLP-1 receptor agonists. So, it suggested a basket approach that weighted the treatment effect of GLP-1 receptor agonists by the proportion of adults with BBS that can access them in the NHS practice. It also recalled that some adults with BBS are using a GLP-1 receptor agonist as a treatment for diabetes. So, setmelanotide could be used as an add-on therapy and there is uncertainty about the additional benefit that would be seen in this setting (see section 3.5). The committee was aware that the BBS specialist centre in Birmingham that had several years of experience of treating BBS in adults using GLP-1 receptor agonists. So, it thought that this was the most relevant potential source of new evidence. If this data could not be accessed or was insufficient, the committee suggested alternative sources. This could be to use published data on the use of GLP-1 receptor agonists in Alström syndrome as a proxy for BBS. The company could also do a structured elicitation exercise with healthcare professionals to determine expected treatment effect on BMI class shift in people with BBS treated with GLP-1 receptor agonists.

The committee also requested more information on the methods and analysis underlying the company's evidence on hyperphagia severity at

baseline in adults, as detailed in section 3.16. The committee concluded it was unable to determine a preferred ICER for the review. It also requested that the company submit additional evidence and analyses on the modelling of hyperphagia and potential use of GLP-1 receptor agonists in adults with BBS to help its decision making.

Committee's preferred ICERs

Preferred ICER for HST31

3.30 Details of the company's and EAG's cost-effectiveness estimates and committee's preferred assumptions can be found in HST31. The committee had agreed to apply a QALY weighting to account for the size of the incremental therapeutic improvement. But, because of considerable uncertainty in QALYs generated in the model, it was appropriate to apply 90% of the weighting (see section 3.25). When considering this, its preferred ICER using the mixed population of children, young people and adults was higher than the threshold normally considered a cost-effective use of NHS resources for highly specialised technologies. The committee recalled that there was a subgroup effect in children and young people. It thought that this warranted consideration of the analyses in which everyone entered the model as children. When applying its preferred assumptions to this population, the ICER was £171,844 per QALY gained. This was within the threshold normally considered cost effective for highly specialised technologies, even when 90% of the QALY weighting was applied.

Preferred ICER for this review

3.31 The committee noted that it had not been able to state a preference for the baseline hyperphagia severity distribution or hyperphagia transitions. It had also requested that the company submit evidence and analysis to enable consideration of GLP-1 receptor agonists as comparators for some adults in the model. So, the committee concluded that it was unable to determine a preferred ICER for people who start treatment as adults. This

meant that it was unclear whether this was below the threshold normally considered an acceptable use of NHS resources in a highly specialised technology when applying a QALY weighting. So, it concluded that setmelanotide should not be used to treat obesity and hyperphagia in people with BBS starting treatment as adults.

Other factors

Equality

3.32 The committee recalled the equality considerations from HST31, which are duplicated here. The committee noted that the population for which setmelanotide is indicated includes children and young people. It recalled that there are greater health benefits for children and young people than for adults with the condition. The committee discussed the need to balance the importance of improving the lives of children and young people, and their families with fairness to people of all ages. It noted the principles that guide the development of NICE guidance and standards. This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The HST31 committee acknowledged and considered the nature of the population as part of its decision making. It noted that its recommendations allowed children and young people to start setmelanotide, but that 40% of the BBS population were assumed to be adults in HST31. The adults would not be able to access treatment. It recalled that the cost-effectiveness estimates in the populations including adults were substantially higher than the threshold normally considered cost effective for highly specialised technologies. So, a negative recommendation in people starting treatment as adults would be proportionate to NICE's legitimate aim to recommend clinical- and cost-effective technologies.

The clinical and patient experts also noted that setmelanotide is self-administered as a subcutaneous injection every day. So, people with

vision problems, learning or physical disabilities and needle phobia might find this challenging. The clinical experts highlighted that the burden of administration would reduce significantly with the new weekly formulation in a prefilled injector. The clinical experts also highlighted that 20% of people with BBS do not have identifiable pathogenic variants on genetic or genomic testing and are identified clinically. The committee noted that genetic confirmation was a requirement in the marketing authorisation for setmelanotide. So, some people with the condition would not be able to access the treatment in the absence of genetic testing. The committee considered that it could not make a recommendation outside of the licensed population.

At consultation for HST31, the company highlighted that additional ethnic minority groups that may be disproportionately affected by BBS. It stated that, as a recessive genetic disorder, BBS disproportionately affects people from ethnic minority backgrounds in which consanguineous marriage is more commonly practiced. Also, people from Black, Asian and other ethnic minority backgrounds have an increased cardiometabolic health risk at lower BMI thresholds than people from a White ethnic background. The committee considered these issues. But it concluded that its recommendations apply equally, regardless of ethnicity, so a difference in condition prevalence did not in itself represent an equality issue. It concluded that all equalities issues for setmelanotide had been considered in its decision making.

In addition, for this review, the committee noted comments from stakeholders that people with limited resources or reduced access to structured support may have greater difficulty managing persistent hyperphagia and obesity. It also noted comments, including those heard in the committee meeting for the review, that access to existing treatments used to manage obesity or diabetes varies between regions. The committee considered these issues. But it concluded that access to NHS

healthcare, specialist services and national commissioning were not implementation issues that could be addressed by a NICE recommendation.

Inequity

3.33 The company highlighted that, for this review, its whole population co-base case provided context to the adult base-case population and avoided inequity concerns. This was because starting setmelanotide later in life does not capture the full potential lifetime benefits of treatment through undiscounted QALY gains. The EAG did not think that the company's co-base case was directly relevant to the decision problem as specified in the NICE scope (see section 3.7). It noted that HST31 had recommended starting setmelanotide in children aged 6 to 17 years but permitted continuation of treatment into adulthood. So, the current evaluation should be focused on adults who do not start setmelanotide treatment as children, rather than a mixed age population. But the EAG agreed that there is an inequity issue for people with BBS who were already adults (18 years or over) before the HST31 recommendations were published and so not able to start treatment during childhood.

The committee understood that some people were adults at the time HST31 recommended setmelanotide for children and young people. It was also aware that, although atypical, some people with BBS may not have a diagnosis until adulthood. Clinical advice to the EAG was that the inequity issue for adults may be mitigated by access to GLP-1 receptor agonists for adults who meet the eligibility criteria for obesity. But a clinical expert at the meeting commented that the inequity in access to a precision treatment for BBS would remain. The committee also understood that there is regional variability in access GLP-1 receptor agonists through specialist weight management services and variation in practice between the 2 BBS specialist adult clinics in England. They heard from a patient expert that primary care practitioners may be unwilling to prescribe a GLP-1 receptor agonist to someone with BBS. The committee

considered these issues. But it recalled its previous conclusion (see section 3.32) that a negative recommendation in people starting treatment as adults would be proportionate to NICE's legitimate aim to recommend clinical- and cost-effective technologies.

Uncaptured benefits

3.34 The company highlighted several potential uncaptured benefits in its modelling, including that:

- the model did not account for natural weight gain in people with BBS having best supportive care
- using a Markov model structure meant people had the same comorbid burden on ending treatment with setmelanotide than people in the model not having treatment with setmelanotide (modelled treatment benefits of setmelanotide on comorbidities were not retained)
- some obesity-related comorbidities (such as metabolic syndrome score) were not captured by the model
- its approach to modelling improved or delayed progression of liver and kidney disease was conservative, including because the costs of dialysis were not included
- setmelanotide may be associated with improvements in cognitive and affective function and these were not captured in the model
- any immunomodulatory benefit beyond weight loss was not captured
- the wider family quality-of-life benefits of reducing hyperphagia
- the financial burden associated with BBS, including indirect costs of obesity on lost work for patients and carers, and higher food bills.

The EAG agreed that the impact of setmelanotide was broader than specific comorbidities that were modelled. But it noted these were already be captured to some extent through utilities and costs associated with higher BMI states. The EAG thought that it was unclear whether there were additional effects on the liver (MASH) and kidney disease beyond those seen through changes in BMI. So, these may

already have been captured for costs and utilities through the BMI categories (see section 3.19 and section 3.20). The EAG also thought that it was unlikely that setmelanotide had additional immunomodulatory effects. It thought that any benefit on cognitive function was uncertain but agreed that this was not captured in model. Its clinical advisers had noted potential benefits may be seen through weight loss (as was seen with GLP-1 receptor agonists) based on some evidence from Germany. The patient expert at the meeting explained that setmelanotide removed the constant food noise, which enabled them to concentrate more, perform better at work, have more energy and socialise more. A clinical expert described findings from their adolescent BBS clinic, where people on treatment had better sleep, improvements in their attention span and concentration, and better education outcomes. The expert added that these benefits were distinct from effects of setmelanotide on hyperphagia. They also noted that parents reported that the family could go to a restaurant to eat out together for the first time without problems. The committee noted that carer HRQoL was captured in the model but that of the wider family may not be. The EAG noted that consideration of the financial burden of BBS was outside the NICE reference case.

The committee decided that some benefits of semaglutide may have been underestimated in the model and some may have been uncaptured. It noted that uncaptured benefits in adults were relevant to the decision problem. It decided that these were likely to include treatment effects on cognition, concentration and sleep, and wider benefits to family life. The committee recalled that there was uncertainty in the modelling (see section 3.26) and that it was unable to determine its preferred ICER for people who start treatment as adults. So, it was unable to take potential uncaptured benefits into account at this time.

Conclusion

Recommendation

3.35 The committee recalled that, for HST31, the ICER using its preferred assumptions in the subgroup in which everyone entered the model as children was below the threshold normally considered cost effective for a highly specialised technology. This was when considering a QALY weighting. So, it could recommend setmelanotide for routine commissioning to treat obesity and hyperphagia only in people with BBS starting treatment aged between 6 and 17 years (with continuation into adulthood if clinically indicated).

For this review, the committee noted that it was unable to determine its preferred ICER for people starting treatment as adults because of the uncertainties and requested analyses. So, it was unclear whether this was below the threshold normally considered an acceptable use of NHS resources in a highly specialised technology when applying a QALY weighting. The committee concluded that setmelanotide should not be used to treat obesity and hyperphagia in people with BBS starting treatment as adults. It also requested that the company submit additional evidence and analyses (see section 3.29) to inform its decision making at the next committee meeting.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Iolo Doull

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

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