# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Draft guidance consultation

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

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: February 2024

**Note that this document is not NICE's final guidance on this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using setmelanotide in the NHS in England.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 manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 14 March 2024
- Fourth evaluation committee meeting: Date to be confirmed
- Details of the evaluation committee are given in section 5

# 1 Recommendations

1.1 Setmelanotide is recommended as an option for treating obesity and hyperphagia in genetically confirmed Bardet-Biedl syndrome (BBS) in people aged 6 years and over, only if they are aged between 6 and 17 when treatment starts. These people can carry on having setmelanotide as adults until they need to stop. Setmelanotide is only recommended 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 clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by them, their clinician, and their parents or carers.

**Why the committee made these recommendations**

BBS is a debilitating rare genetic condition that severely affects the quality of life of people with the condition, their families and carers. It causes hyperphagia (characterised by a feeling similar to starvation), which can lead to early onset severe obesity and affects many different parts of the body. These symptoms are managed with best supportive care, which includes dietary restrictions and lifestyle changes, including exercise.

Results from clinical trials suggest that setmelanotide may reduce weight and body mass index (BMI) in people aged 6 years and over. There seems to be more benefit for people who start setmelanotide aged between 6 and 17 years than people who start as adults. The clinical trial results also suggest that hunger scores and quality of life are improved with setmelanotide in the short term, although hunger scores may not reliably reflect changes in hyperphagia. Follow up in the trials is short, so the long-term effects of setmelanotide are uncertain.

There are also uncertainties in the economic model. Some benefits of setmelanotide may not have been captured adequately and some may have been overestimated in the cost-effectiveness analysis. So, the size of any uncaptured benefits is unknown. In the population of adults and children (which reflects the current population in the NHS), the uncertainties in the evidence mean that the cost-effectiveness estimates for setmelanotide are higher than what NICE normally considers an acceptable use of NHS resources within the context of a highly specialised technology. But setmelanotide is estimated to be cost effective in people who start taking it aged between 6 and 17 years. So, setmelanotide is recommended for these people.

# 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 6 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 per 10 mg/ml vial for injection (excluding VAT; BNF online, accessed July 2023).

2.4 The company has a commercial arrangement (simple patient access scheme). This makes setmelanotide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 3 Committee discussion

The evaluation committee considered evidence submitted by Rhythm Pharmaceuticals, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

## The condition

### Bardet-Biedl syndrome (BBS)

3.1 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. 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

3.2 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 for later eating. A patient expert explained that, before taking 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. The committee concluded that BBS has a substantial impact on people with the condition, their families and carers.

## Clinical management

### Treatment options

3.3 There are no licensed treatments for obesity and hyperphagia caused by BBS, and there are no treatments that reduce hyperphagia. So, best supportive care for obesity includes dietary advice to manage the hyperphagia and exercise modification. One patient expert highlighted that restricting calorie intake in a child with hyperphagia is extremely hard to manage. Carers face an “endless battle” over food and must take extreme measures, such as locking food cupboards, to limit intake. The clinical experts explained that the standard interventions are rarely effective in the long term because they do not address the underlying hyperphagia. The committee concluded that there is an unmet need for a new treatment for the condition.

### Relevant comparators

3.4 The committee understood that the NICE scope also included bariatric surgery as a comparator, but that it was excluded from the company's submission. The clinical experts explained that, although bariatric surgery has been used to treat BBS in the past, the outcomes are variable and tend to be worse than outcomes for people living with general obesity. Hunger generally increases after surgery, and lifelong follow up with nutritional support is needed. So, bariatric surgery can exacerbate existing hyperphagia in people with BBS because the MC4R pathway remains disrupted. Also, even in people living with general obesity, only a small proportion have surgery because it is inappropriate for people with certain comorbidities. So, the committee 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 semaglutide for treating general obesity in adults. The clinical experts 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 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.

## Decision problem

### Company's population

3.5 The committee noted that the company had limited its population in the decision problem to only people with severe hyperphagia who would be expected to benefit most from setmelanotide. The EAG highlighted that there was no validated and standardised assessment tool to measure hyperphagia in people with BBS. It also noted that it was unclear how

hyperphagia would be consistently and accurately categorised in clinical practice. Without a means of consistently identifying people with severe hyperphagia, it is possible that setmelanotide will be used in people with moderate hyperphagia. At technical engagement, the company explained that people with BBS have treatment at specialist centres with clinicians experienced in the condition. The clinical experts agreed that severe hyperphagia would be identifiable by a person's weight, and by maladaptive and extreme food-seeking behaviour. This behaviour includes eating to the point of vomiting and taking food from bins. They highlighted that the extreme level of obesity in small children with severe hyperphagia makes BBS in them easy to identify. They noted that some of them will have sleep apnoea. A patient expert highlighted that a multidisciplinary team including clinicians, psychologists and nutritionists contribute to the diagnostic process. They build a relationship to establish the severity of eating habits for a particular person. But even moderate hyperphagia can significantly affect the quality of life of people with BBS and their carers. The committee considered the definitions of mild, moderate, and severe hyperphagia that had been provided by the company as part of a vignette to collect utility data (see section 3.19).

At the second committee meeting, 1 clinical expert stated that the description of behaviours in the vignette was appropriate for capturing the differences between hyperphagia severities. They stressed the lack of established scoring systems for most behavioural aspects of condition. But the committee remained concerned that some people with moderate hyperphagia would have setmelanotide in clinical practice. It thought that, despite the clinical expert support for the company's vignette, the definition between severities seemed quite subjective. It also noted that there is no standardised severity scale used in clinical practice. It recalled that identification of hyperphagia severity relies on clinical judgement, and that severe hyperphagia was not an inclusion criterion in the clinical trials. The committee concluded that there was uncertainty about:

- the proportion of people with severe hyperphagia as envisaged in the company's decision problem
- whether it would be possible to consistently identify these people in clinical practice.

So, it concluded that the whole population in the marketing authorisation, which would likely be a mixture of people with moderate and severe hyperphagia in clinical practice, should be considered for decision making.

## Clinical effectiveness

### Data sources

3.6 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 aged 6 years and over with a body mass index (BMI) of 30 kg/m$^2$ or over (or the ninety seventh percentile or more in people under 16 years). Twenty two people were randomised to placebo and 22 people 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. Results are available up to week 89. No further data is expected for people with BBS. The committee concluded that RM-493-023 and RM-493-022 were the most appropriate data sources to inform the clinical effectiveness of setmelanotide.

## Generalisability

3.7 The committee noted that the company's clinical trials were small and included only 2 people from the UK. Because of this, the EAG highlighted that the population in the clinical trial may lack generalisability to the BBS population in clinical practice. It suggested comparing the trial baseline characteristics with people from the UK in the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS). But the company stated there were too few people with BBS from the UK enrolled in CRIBBS to provide useful data for comparison. The EAG also noted discrepancies between people with 52 weeks of follow up compared with people with less, and between people in the supplemental cohort compared with the pivotal cohort. The clinical experts stated that baseline characteristics for people with BBS were unlikely to differ by location and that the trial population was generalisable to the people they would expect to see in clinical practice. The committee recalled that the company's population included only people with severe hyperphagia (see section 3.5). The company explained that, because there was no validated or standardised instrument for measuring hyperphagia, severe hyperphagia was not an

inclusion criterion in the clinical trials. It highlighted that people in the trial had a BMI of 30 kg/m$^2$ or over, a level of obesity suggesting severe hyperphagia. But the committee was concerned that some people might have a BMI of this level without having severe hyperphagia. The clinical experts agreed that this was plausible because people living with general obesity (not associated with hyperphagia) may have a BMI of 30 kg/m$^2$ or over. So, the committee agreed that the company's clinical trial populations likely included a mixture of people with different levels of hyperphagia severity. But it recalled that setmelanotide would likely be used in people with a range of hyperphagia severities in clinical practice (see section 3.5). It concluded that RM-493-023 and RM-403-022 were likely generalisable to the BBS population in clinical practice.

## Obesity-related outcomes

3.8 The primary outcome in the RM-493-023 study was the proportion of people having at least 10% weight loss with setmelanotide from baseline to 52 weeks. This was in people with BBS aged 12 years and over who were compared with an historical control rate of 10% from the CRIBBS registry (the results are confidential and cannot be reported here). It was assessed in the full analysis set in the pivotal cohort, defined as people who had at least 1 dose of setmelanotide and were evaluated at inclusion. The committee noted that the trial included people with BBS and Alstrom Syndrome, but only considered results in the BBS population. Results at 14 weeks showed a non-statistically significant difference between setmelanotide and placebo. The mean reduction in weight at week 52 in the BBS population in the pivotal cohort was 9.4 kg (8%). The company also presented subgroup analyses for the primary outcome in people aged 18 years and over. When compared with the CRIBBS historical control rate, 46.7% of people aged 18 years and over had a reduction in weight from baseline of 10% or more at week 52 (95% confidence interval [CI] 21 to 73, p=0.0003). For people under 18 years, the company preferred to use BMI-Z scores to characterise obesity. This is because

BMI-Z scores are linked to sex and age, so account for natural growth in this population. In RM-493-023, 85.7% of people aged 6 years to 17 years (from here, referred to as children and young people) in the pivotal cohort (full analyses set) had a 0.2-point reduction in BMI-Z score or more at week 52. The EAG highlighted that the observed treatment effect was larger in children and young people then in adults. There was also variability in the size of the change, especially for children and young people. The committee concluded that setmelanotide likely improves obesity-related outcomes in the short term, but that the results were associated with uncertainty.

## Other key clinical outcomes

3.9 RM-493-023 also considered hunger and quality of life as key clinical outcomes. At week 52, there was a 31% improvement in worst hunger score for people aged 12 years and over without cognitive impairment in the pivotal cohort (standard deviation 26, p=0.0004). Of these, 57.1% had a reduction in their daily hunger score of 25% or more (p<0.0001). Improvements in quality of life were seen for the Impact of Weight on Quality of Life (IWQOL)-Lite scores in adults and Paediatric Quality of Life Inventory (PedsQL) scores for children and young people. EQ-5D-5L scores were also collected in RM-493-023 in people aged 12 years and over without cognitive impairment and showed improvements in the mean change score. The committee noted that quality of life of carers had not been collected in the trial, and that there were no results from 14 weeks reported in the company submission. At consultation, the company submitted an analysis of metabolic outcomes after 52 weeks of setmelanotide from RM-493-023. The results suggested a decreased risk of metabolic syndrome, which is associated with cardiovascular conditions and type 2 diabetes in people whose BBS responded to setmelanotide compared with people whose condition did not (exact results are confidential so cannot be reported here). The committee agreed that the company's new evidence supported the clinical effectiveness of

setmelanotide in the short term. But it noted the small numbers in the analysis. It concluded that setmelanotide likely improves hunger and metabolic outcomes in, and the quality of life of, people with BBS in the short term, but that the results were uncertain.

### Potential bias in RM-493-023

3.10 The EAG highlighted that the week 52 results in RM-493-023 were not based on a randomised controlled comparison. Instead, people were compared with their baseline data. Because of this, it was concerned that the observed treatment effect may not have been caused by setmelanotide alone. It also noted that people in the placebo arm had a reduction in maximum hunger score and BMI during the titration and retitration periods. It highlighted that this may represent a regression to the mean or a placebo effect. The company stated that weight, BMI and hunger scores were virtually unchanged in people on placebo during the 14-week randomised controlled period, so adjustment for regression to the mean was not needed. But the committee noted a larger treatment effect after 52 weeks of follow up in people initially randomised to setmelanotide than people initially randomised to placebo. At consultation, the company submitted analyses that showed the change in BMI-Z from children and young people whose condition responded to treatment in RM-493-023 when adjusted for a placebo effect (exact results are confidential so cannot be reported here). The committee agreed that this approach was more likely to reflect the true treatment effect of setmelanotide. It concluded that 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.

### Long-term treatment effects

3.11 The committee 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 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. It concluded that the long-term treatment effects of setmelanotide were uncertain.

### Stopping treatment

3.12 The company defined response to treatment after 52 weeks of setmelanotide as:

- a 10% or more reduction in weight in adults
- a 0.2 or more reduction in BMI-Z-score in children and young people.

The committee noted that the company's response criteria did not consider people for whom there was a reduction in hyperphagia but no reduction in weight. The clinical experts explained that, although BMI and hyperphagia were somewhat correlated, a small proportion may have reduced hyperphagia but limited weight loss. This may be caused by a change in eating habits or using other medications that promote weight gain that is slower than the change in hyperphagia. Because reducing hyperphagia is likely to considerably increase quality of life, these people may want to continue setmelanotide. So, response was likely to be assessed as a change in the behaviours associated with severe hyperphagia (see section 3.5).

At the second committee meeting, the company explained that, although its response rates used data from week 52 of RM-493-023, response to setmelanotide would be assessed earlier in clinical practice. This was because there was a delay between response in hyperphagia and weight. The clinical experts explained that changes in hyperphagia indicating a

treatment response would be evident after 14 weeks. This was based on data from RM-493-023, in which a marked decrease in hunger scores could be seen by 14 weeks of setmelanotide in people whose condition responded to treatment. The company stated that people without a hyperphagia response within the first 3 months were unlikely to have a change in eating habits to allow a reduction in BMI after 52 weeks of treatment. One clinical expert confirmed that, based on their experience with setmelanotide and other weight loss drugs, they would stop treatment if there was no effect on hyperphagia after 14 weeks. They explained that there are no formal response criteria. But they said that the decision to stop setmelanotide would be made by a multidisciplinary team of weight loss specialists, psychologists and dieticians alongside local weight loss clinics. The committee agreed that behavioural changes are important markers of response to treatment. It concluded that, in clinical practice, response to setmelanotide would be assessed at 14 weeks by a multidisciplinary team.

## 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 committee concluded that the company's model structure based on BMI classes was acceptable for decision making.

## Population in the model

3.14 In its base case presented at the first 2 committee meetings, the company assumed that all people started setmelanotide as children. The model starting age was 6 years, in line with the marketing authorisation. It also provided subgroup analyses that assumed:

- either everyone entered the model as adults, or
- a mixed population was included, in which 60% of the population entered the model at age 6 years and 40% at age 18 years, reflecting the proportion of adults and children in the NHS according to the company's clinical expert advice.

The clinical experts at the committee meeting stated that the mixed population may still have overestimated the proportion of children with BBS in current clinical practice. But the company highlighted that, in the future, it expected setmelanotide to be started in childhood. This is because BBS is clinically identifiable at an early age, with around 90% of people with the condition having obesity by age 5 years. Also, people are likely to start treatment earlier in the future because:

- genetic screening will be expanded
- clinicians will prefer to treat BBS early to prevent long-term complications of obesity.

The clinical experts stated that, although early diagnosis was improving, tools for diagnosis were still limited. For this reason, a substantial proportion of people are diagnosed and start treatment for BBS as adults in current clinical practice. They highlighted that BBS is a complex condition, and several of the associated comorbidities, such as intellectual disabilities, may be absent or occur later for some people. So, these people might not be diagnosed until adulthood. The EAG's clinical experts

stated that it would likely be many years before everyone with BBS was diagnosed as children. This was supported by 1 clinical expert at the second meeting. They stated that, in their experience, most people seen in BBS clinics are adults or young people, although the exact proportions are uncertain. The committee acknowledged that diagnosis in childhood may increase in the future but that this would likely be slow. After the third committee meeting, the company requested that the committee consider a recommendation in people who start setmelanotide as children. The committee noted that this subgroup did not reflect the total population in the NHS. In line with the NICE health technology evaluations: the manual, the committee considered whether there was a difference in treatment effect by age:

- RM-493-023 and RM-493-022 did prespecified subgroup analyses in people aged 6 to 17 years.
- More children and young people than adults met the response criteria in RM-493-023.
- Children and young people had a larger BMI class drop than adults in RM-493-023.

The committee acknowledged that there was likely a larger treatment effect in children and young people than in adults. It agreed that a subgroup effect in children and young people was biologically and clinically plausible. This was because treating BBS early may improve outcomes by reducing long-term weight gain and complications of obesity such as metabolic syndrome, cardiovascular disease and diabetes. The company also highlighted that children and young people need a higher number of carers than adults with BBS (see section 3.21). So, the committee agreed that the company's subgroup could be considered separately. The committee concluded that it was appropriate to use the scenario that best represented current clinical practice in decision making, while noting the uncertainty in the distribution of adults and children. So, it

preferred the mixed population but also considered subgroup analyses in which everyone entered the model as children.

### Baseline hyperphagia status

3.15 The company's original submission assumed that all people with BBS had severe hyperphagia at baseline (see section 3.5). The committee noted that the challenges of differentiating between moderate and severe hyperphagia meant that:

- some people with moderate hyperphagia would likely have setmelanotide in clinical practice (see section 3.5)
- a mixture of hyperphagia severities was likely included in the trial population (see section 3.7).

So, at the first and second meetings, the committee preferred an EAG scenario that assumed 60% of people had severe and 40% had moderate hyperphagia at baseline. This scenario was based on the results of a survey by BBS UK quoted by the company in its original submission.

After the committee's second meeting, the company verified that this survey included people with BBS regardless of whether they had obesity. It highlighted another BBS UK survey, which reported that 70% of all people with BBS have obesity. The company assumed that everyone with severe hyperphagia would have obesity, so 60% of the BBS population would have obesity and severe hyperphagia, 10% obesity and moderate hyperphagia, and 30% no obesity and moderate hyperphagia (latter group not covered by setmelanotide's marketing authorisation; see section 2.1). In the modelled population (that is, people with BBS and obesity), these proportions translated to 86% of people having severe hyperphagia and 14% having moderate hyperphagia at baseline. The EAG highlighted that these calculations assumed that no one with BBS had mild hyperphagia. They would also imply that 75% of people with moderate hyperphagia did not have obesity. The clinical experts noted that people with BBS have

access to specialist care that can help them maintain their weight. They also explained that obesity is a chronic condition, and that the BBS UK surveys did not consider change over time. But the EAG highlighted that the utility values in the model suggested a relatively high quality-of-life decrement for people with moderate hyperphagia. So, it was unlikely that 75% of people with moderate hyperphagia would not have obesity. For its base case, it preferred the company's scenario that assumed that 75% of people had severe and 25% had moderate hyperphagia at baseline. The committee was concerned that the results from the BBS UK hyperphagia survey may have overestimated the proportion of people with severe hyperphagia. This was because the definitions of severe hyperphagia in the BBS UK survey and the vignette were not aligned. The committee noted that some of the descriptions of severe hyperphagia in the survey, as given by the clinical expert representing BBS UK, overlapped with the company's vignette descriptions for moderate hyperphagia (see section 3.5). That is, some people classed as having 'severe' hyperphagia in the BBS UK survey would have been classed as having 'moderate' hyperphagia in the model. So, the committee was concerned that the results may not have been generalisable to the company's model. The committee also noted that the proportion of people with severe hyperphagia at baseline depended on the assumed proportion of people with BBS living with obesity. It noted that 30% of people were reported as not having obesity in the BBS survey headline results. This included 12% who reported mild obesity and 18% who reported that this was not applicable. So, the proportion of people with BBS who have obesity in clinical practice could be higher than 70%. This aligned with other literature sources, such as Forsythe et al. (2023), in which 88% of adults in a multinational survey of people with BBS had obesity. When using this data, the percentage of people with severe hyperphagia was closer to the EAG's preferred 75% of the modelled population. The company justified using the BBS UK surveys to inform the hyperphagia severity distributions. This was because both surveys were recent and had been

carried out in the same UK population. It highlighted that sources reporting higher obesity levels may be associated with higher proportions of severe hyperphagia than reported in the BBS UK data. The committee agreed that the company's preferred distributions likely overestimated the proportion with severe hyperphagia. It considered that even the EAG's preferred split of 75% to 25% severity levels could have overestimated how many people would have severe hyperphagia at baseline when using the vignette definitions of moderate and severe hyperphagia. The committee concluded that the distribution of hyperphagia severity levels at baseline was unknown. It acknowledged that hyperphagia has a large impact on the quality of life of people with the condition and their carers, regardless of the severity (see section 3.2). But, of the options it was presented with, it preferred the assumption that 75% of people had severe and 25% had moderate hyperphagia to illustrate the BBS population entering the model.

### Modelling treatment effect on BMI-Z in children

3.16 The company used data from RM-493-023 to inform the following model inputs:

- the distribution of people in each of the 7 BMI and BMI-Z health states at baseline
- the response rates for setmelanotide at 14 weeks (see section 3.12); the committee noted that the results from 52 weeks were used to inform response to setmelanotide at 14 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.

At the first committee meeting, the company applied the most frequently seen BMI and BMI-Z class shifts to people whose condition responded to treatment. The EAG noted that children and young people had a larger reduction in classes than adults (exact class drops are confidential and cannot be reported here). It highlighted that the BMI-Z class shift in children may have been overestimated. It noted that Forsythe et al. (2021)

reported a mean change in BMI-Z score of -0.7 kg/m$^2$ for 9 children from RM-493-023. This translated to a class shift smaller than that modelled by the company. This was preferred by the EAG and committee at the first meeting. The company highlighted that its chosen BMI-Z class cut offs had larger intervals at the extremities (less than 2 and over 4) than values used in the middle. It noted that using more granular classes to capture BMI-Z scores over 4 increased the mean shift in classes from the trial. This suggested its model may have underestimated the impact on setmelanotide in people with a very high baseline BMI-Z score. Also, RM-493-023 did not allow dietary and exercise modifications in either study arm. And these would likely be used in combination with setmelanotide in clinical practice and may convey some additional benefit.

At consultation, the company updated its base case to use a weighted average of class shifts equivalent to the mean BMI-Z change in the trial when all classes, including those of BMI-Z scores over 4, were equally distributed. A second analysis applied an adjustment for a placebo effect to the weighted average from the trial. This was preferred by the EAG for its base case. The committee acknowledged that adjustments for the placebo effect cancelled out any uncaptured benefit from the exclusion of dietary and exercise modifications in the trial. It noted that both estimates using the weighted average approach were between the EAG's and company's preferred assumptions at the first committee meeting. But it noted that adjusting for a placebo effect resulted in a slightly smaller BMI-Z class shift (exact inputs are academic in confidence and cannot be reported here). The committee acknowledged that the treatment effect in people with very high BMI-Z scores may have been underestimated because of the class cut offs used. It noted that the company had chosen these cut offs based on the available comorbidity data. It was concerned that using more granular categories above a BMI-Z score of 4 would disassociate the treatment effect from the cost and resource inputs for the modelled health states. But it acknowledged that, by using a weighted

average approach, the model somewhat captured the variability seen for BMI-Z score changes in the trial. It also recalled its preference for using results that adjusted for a potential placebo effect (see section 3.10). The committee concluded that the company's modelling of treatment effect on BMI-Z risked adding uncertainty. But it concluded that it was most appropriate to model the BMI-Z class shift using the weighted average from the trial adjusted for a placebo effect.

### Modelling treatment effect on hyperphagia

3.17 At 14 weeks, the company assumed that all people whose condition responded to setmelanotide transitioned to mild hyperphagia. This was regardless of their hyperphagia severity when they started in the model and independent of change in BMI-Z or BMI. It was based on feedback from people who met the primary outcome in RM-493-023. It was also based on the view that the extent of weight loss seen in the trial could only have been caused by a transition to mild hyperphagia and the resultant change in eating habits. One patient expert supported this assumption, stating that their hyperphagia, which was previously severe, had greatly reduced when having setmelanotide. The EAG highlighted the variation in BMI-Z and worst hunger score changes in RM-493-023. It explained that this suggested that some people remained at a moderate level of hyperphagia when their condition responded to setmelanotide (see section 3.8 and section 3.9). In its base case after consultation, the EAG modelled people whose condition responded to treatment as people with:

- severe hyperphagia at baseline moving to both mild and moderate hyperphagia, based on the proportions in RM-493-023 moving 2 BMI-Z class levels for moderate hyperphagia and 1 BMI-Z class level for mild hyperphagia (exact proportions are confidential and cannot be reported here)
- moderate hyperphagia at baseline moving to mild hyperphagia.

At consultation, the company introduced scenarios in which people moved to no hyperphagia after treatment (that is, no quality-of-life decrement for hyperphagia was assumed in the model). But the committee noted the relatively small change in hunger score reported in RM-493-023 for people having setmelanotide. The committee understood from the patient and clinical experts that hyperphagia is much more than hunger. But it noted that the company vignettes used to classify hyperphagia severity included behaviour related to hunger in several of the criteria. The clinical experts explained that treatment response in obesity is complex, and that there is a lack of data to inform setmelanotide's effect on hyperphagia. But they expected setmelanotide to have a large effect on hyperphagia because, unlike other BBS treatments, it restored the deficient MC4R pathway. For the third committee meeting, the company provided further clinical expert statements. These supported the assumption that some people with moderate hyperphagia at baseline or with severe hyperphagia and a large reduction in BMI-Z score would be expected to have no hyperphagia with setmelanotide. But the committee was concerned that the moderate decrease in hunger seen in the trial was hard to align with the company's scenarios including a no hyperphagia state. So, it was not convinced that it had enough evidence to accept scenarios in which people transitioned to no hyperphagia.

At the second committee meeting, the company highlighted that the EAG's modelling may have underestimated the number of people moving from severe to mild hyperphagia. This was because it did not account for the more granular classification of BMI-Z classes above a score of 4 (see section 3.16). The EAG acknowledged this but highlighted that the trial classed response to treatment as a minimum 0.2 reduction in BMI-Z score. So, it was possible for people's condition to be classed as responsive while they remained in their baseline BMI-Z health state. The EAG noted that this was the case for all people in RM-493-023 whose BMI-Z score did not decrease the company's preferred BMI class change

or over when using more granular BMI-Z health states over 4. When assuming these people remain with severe hyperphagia after treatment but everyone else with severe hyperphagia at baseline moved to mild hyperphagia, there was very little difference between the analyses that did and did not adjust the BMI-Z classes over 4. The EAG also noted that these estimates did not account for the placebo effect so may have been overestimated.

After the second committee meeting, the EAG provided analyses in which people whose condition responded to setmelanotide but who did not have a shift in BMI-Z class moved from severe to moderate hyperphagia after treatment. This was based on company and clinical expert testaments that people in the trial with a large enough BMI-Z score drop to be classed as having had a response would see some reduction in hyperphagia. The committee agreed that there was substantial uncertainty about the treatment effect on hyperphagia because it was not measured in the trials. It acknowledged that reducing hyperphagia, even slightly, would have a large impact on the quality of life of people with BBS and their carers. It would allow them to lose weight through maintaining a healthy diet and exercise regime. This could, in turn, improve self-esteem and obesity-related comorbidities (see section 3.2). But the committee was concerned that the improvements in hyperphagia included in the company's model were based on expert opinion alone. It thought that this made a large contribution to improvement in quality of life, rendering the model results highly uncertain. It preferred to use trial data to inform transitions when possible, even though separate assumptions were needed for this. It acknowledged that the EAG's base case at the second committee meeting had limitations because it:

- used BMI as a proxy for hyperphagia and the correlation between these outcomes is uncertain (see section 3.12)

- may have underestimated the proportion of people moving from severe to mild hyperphagia by not including more granular classes over a BMI-Z score of 4.

The committee recalled that a small proportion of people may have reduced hyperphagia but limited weight loss (see section 3.12). It noted that this aligned with the EAG's scenario in which people without a BMI-class drop in RM-493-023 moved from severe to moderate hyperphagia. This scenario also used the more granular classes over a BMI-Z score of 4. The committee noted the uncertainty in all the hyperphagia transition estimates. But, it preferred the scenario in which people without a BMI-class drop in RM-493-023 moved from severe to moderate hyperphagia for decision making.

### Long-term treatment effect

3.18 After the initial response at 14 weeks, the company assumed that people in the model maintained their BMI or BMI-Z classes while on treatment. That is, there was no waning of treatment effect. As a proxy for treatment waning not leading to immediately stopping treatment, the company included an annual 1% stopping rate in people whose condition responded to setmelanotide. This was in line with NICE's highly specialised technology guidance for setmelanotide for treating obesity caused by pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiencies. But the EAG was concerned that the long-term stopping rates may be higher in clinical practice. This was because over 1% of people stopped setmelanotide in RM-493-023 because of a lack of effect (exact rates and confidential and cannot be reported here). Based on this, the committee preferred a stopping rate of 2% at the first meeting.

At consultation, the company highlighted that people who stopped setmelanotide in RM-493-023 because of a lack of effect were already classed as people whose treatment had not responded ('non-responders') in the model. This was because they had limited weight loss and no

change in hunger scores. So, these people were modelled to stop setmelanotide at 14 weeks and should not be counted in the annual stopping rate. The company anticipated that these people would also be easily identifiable early in clinical practice. This was because they would not have the marked change in hunger scores seen by 14 weeks in the clinical trials in people whose condition responded to treatment. Because of this, the EAG updated its base case after consultation to include a 1% stopping rate but noted the uncertainty in the company's estimates. The clinical experts explained that the ongoing treatment effect for setmelanotide is uncertain because it is a new class of drug with little available long-term data. But, without treatment, people with BBS steadily gain weight, so even a plateau of weight loss would be beneficial. The committee recalled that a marked decrease in hyperphagia was expected in people whose condition responded to treatment (see section 3.12). The clinical experts explained that reducing hyperphagia has a big quality-of-life benefit. But they added that hyperphagia is expected to return quickly after stopping treatment, so people are motivated to continue taking a treatment that provides benefits only when taking treatment. The patient expert confirmed this, stating that their hunger massively increased on stopping setmelanotide. The committee agreed that the proportion stopping setmelanotide was likely to be small but that some people may stop treatment because of the need to self-inject every day. It concluded that the exact annual stopping rate for setmelanotide was unknown. But it acknowledged the company's rationale that trial data should not be used to inform this. So, the committee concluded that an annual stopping rate of 1%, although uncertain, could be used in decision making.

## Utility values

### Source of obesity-related utility values

3.19 The committee was aware that quality-of-life data had been collected in RM-493-023. But, at the first committee meeting, the company stated that the quality-of-life instruments used in the trial (PedsQL, Impact of Weight

on Quality of Life-Lite and EQ-5D) lacked the sensitivity to capture the full effect of hyperphagia. Instead, for hyperphagia, it used utility multipliers associated with severity status (mild, moderate and severe) derived from a vignette study in the general public. For each of the 7 BMI health states, utility values came from a US study of Short Form Survey (SF)-12 utilities according to BMI by Alsumali et al. (2018). Utility values for the 7 BMI-Z health states came from Riazi et al. (2010). These values were mapped to EQ-5D-3L using a mapping algorithm from Khan et al. (2014). The EAG highlighted that, although the company's utility values had been accepted in NICE's highly specialised technology guidance for LEPR or POMC deficiency, Forsythe et al (2023) had recently published PedsQL results from RM-493-023. These were collected data from people with BBS instead of general obesity. At technical engagement, the company provided a scenario that mapped the PedsQL data from RM-493-023 to EQ-5D estimates. The EAG noted that the company scenario had not applied the mapping algorithm from Khan et al. correctly and corrected this error. The EAG suspected that this error likely applied to values mapped from Riazi et al. in the company's base case as well. At consultation, the company provided a scenario that corrected this error. At the first committee meeting, the committee preferred to use utility values from Riazi et al. for BMI-Z health states. This was because they were based on 96 children living with obesity, whereas the EAG's mapping was based on 5 people with BBS. One of these 5 informed the lowest BMI-Z health state (BMI-Z scores 0 to 1). The other 4 informed the highest (BMI-Z score over 4), with the utilities for the middle BMI-Z health states extrapolated. So, because there was only 1 person informing the lowest health state, any variation in baseline PedsQL score from the general BBS population could have biased the extrapolated values. After consultation, the EAG updated its base case to use values mapped from the literature, but the company revised base case used values mapped from RM-493-023. The EAG was unclear about why the company chose to use a source of utility values that differed from that preferred by the

committee. It noted that the company had not provided the utility values for its scenario that corrected the mapping of literature values. So, it used the uncorrected values provided by the company at the first meeting. At the second committee meeting, the committee reconsidered this but maintained its preference for utility values from the literature. It acknowledged that the NICE health technology evaluations: the manual specifies a preference for using trial-based utilities when available. But, given the uncertainty introduced by the small sample size (n=5) from the trial available for mapping, the committee agreed that this constituted an exceptional circumstance. The committee would have preferred to use the utilities from the literature that used the corrected mapping approach. But, given that the company did not provide these, it concluded that utilities from the EAG's base case were appropriate for decision making.

### BBS utility multiplier

3.20 At the first meeting, to capture the impact of those features of BBS not related to obesity (such as visual impairment and learning difficulties), the company applied a multiplier of 0.8 to the utility values in the BMI health states of the economic model. This stopped people whose condition responded to setmelanotide having a quality of life equal to that of the general public. The patient experts highlighted the considerable burden of non-obesity-related comorbidities. They stressed that learning and communication difficulties, and visual impairment significantly affect the quality of life of people with BBS (see section 3.2). But the committee was concerned that the company's BBS multiplier was based on an arbitrary value instead of one based on clinical evidence. The committee recalled its preference to use literature-based values from general obesity for baseline BMI health state utilities (section 3.19). It considered the multipliers derived from PedsQL data in RM-493-023. It recalled the error in the company's mapping (see section 3.19). Also, it noted that only 1 person informed the EAG's mapped utility estimates from the PedsQL data in RM-493-023 for the lowest BMI-Z health state. It was concerned

that, if this person had non-obesity-related comorbidities not typical of the condition, it would have skewed the extrapolated values. This meant that they might not have accurately represented the quality-of-life effect. Nevertheless, in this case, it considered the PedsQL derived multiplier values had some advantages because they were based on trial evidence and not an assumption. The committee acknowledged that the effect of non-obesity-related comorbidities on the quality of life of people with BBS was uncertain. But, when considering the analyses presented, it preferred the EAG's preferred assumption using the corrected BBS multiplier based on PedsQL data from RM-493-023 for decision making.

### Carer disutility

3.21 The company applied a disutility of 0.0986 for carers of people with BBS in its base case. This was applied only for people having best supportive care. The committee agreed that this was appropriate because setmelanotide would likely improve quality of life for carers when hyperphagia was reduced in the person with BBS. The patient experts confirmed this, stating that controlling diet and food-seeking behaviours constitutes a large proportion of the care needed, particularly for younger people with BBS. In its base case, the company assumed an average of 1.5 carers per child or young person with BBS. After technical engagement, the number of carers per adult was based on another survey by BBS UK. This captured details of care for 121 adults with BBS (the exact value is confidential so cannot be reported here) but was not provided by the company for EAG critique. This was accepted by committee at the first meeting. At consultation, the company increased the number of carers for adults with severe hyperphagia to 1.5 and maintained the estimate from the BBS UK survey for people with moderate hyperphagia. It then took a weighted average based on the assumed proportion of people with moderate and severe hyperphagia in its base case (see section 3.15). The company justified this approach based on:

- the discussion at the first committee meeting
- a publication by Forsythe et al. (2023) that suggested around 90% of people with BBS have more than one person involved in care.

The committee noted that the average age of the people with BBS in Forsythe et al. was 12 years, so the results were more applicable to children with BBS than adults. The clinical experts stated that the level of care needed for BBS varies enormously between people and over time. But care for adults can be similar to that for children. A patient expert explained that it was hard to disentangle the care needed for hyperphagia from the other components of BBS. But, in their experience, hyperphagia affects the whole family because eating times and food storage need to be considered. This is unlike the other components of BBS for which there is usually 1 main carer. The committee acknowledged the high quality-of life-burden for carers from hyperphagia associated with BBS (see section 3.2). But it noted that the company did not sufficiently justify including multiple carers in the model. It also noted that NICE's highly specialised technology guidance for LEPR or POMC deficiency, which also causes hyperphagia, assumed 1 carer per person with the condition. So, the committee concluded that the assumption of 1 carer per adult with BBS in the model was reasonable for decision making.

## Costs and resource use

### Ongoing monitoring of setmelanotide

3.22 The clinical experts explained that NICE's clinical guideline on identification, assessment and management of obesity recommends a tier-based system of obesity treatment. In its base case, the company assumed setmelanotide would be prescribed in specialist care (tiers 3 and 4) but monitored in primary care (tiers 1 and 2). The EAG stated that setmelanotide would likely be monitored in local weight management clinics in secondary care, supported by specialist BBS centres. It included the cost of secondary care weight management clinic visits in its base

case. The clinicians at the committee meeting supported this, explaining that specialist centres would communicate with local tier 3 obesity clinics to coordinate the care of a person with BBS. They also highlighted that people with BBS often have limited mobility, so some level of local care is important to support with side effects and comorbidities. After consultation, both the company and EAG base cases included the cost of additional visits in their models. The committee concluded that ongoing monitoring for setmelanotide would likely take place in local tier 3 obesity clinics in secondary care.

## Comorbidities

3.23 The company included a cost and disutility associated with common obesity-related comorbidities in its base case. At the first committee meeting, it used prevalence rates for comorbidities taken from people with general obesity using various literature sources. At consultation, it submitted data from a separate model developed to assess the impact of early onset obesity (EOObesity) on outcomes. This suggested that:

- early onset obesity resulted in higher risks for comorbidities and mortality than those from the literature (exact results are confidential and cannot be shared here)
- setmelanotide was associated with lower comorbidity and mortality risk compared with best supportive care, especially when treatment was started early.

At the second committee meeting, the company provided a scenario that used the updated comorbidity and mortality risks in its cost-effectiveness model. The EAG was concerned that the EOObesity model sourced data from studies outside of the UK. It also included the effect of obesity on cancer, which was excluded in the company's cost-effectiveness analysis for setmelanotide. The company did not provide the EOObesity model for critique, so it was unclear how the effect of age and duration of obesity on comorbidities had been modelled. The committee considered that it would

prefer to use data from people with BBS than general obesity. It also agreed that to use the estimates from the EOObesity model might be inappropriate because it had not been fully critiqued by the EAG. The committee concluded that the risk of comorbidities may have been underestimated in the company's base case. But it added that, because of the uncertainty in the EOObesity model, it preferred the literature values for decision making.

## Quality-adjusted life year (QALY) weighting

### Criteria for applying a QALY weighting

3.24 The committee understood that NICE health technology evaluations: the manual (2022) specifies that a most plausible incremental cost-effectiveness ratio (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 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 including:

- the baseline hyperphagia severity distributions (see section 3.15)
- setmelanotide's treatment effect on BMI and hyperphagia (see section 3.16 and section 3.17)
- the stopping rate (see section 3.18)
- the weighting for non-obesity-related comorbidities (see section 3.23)
- the quality-of-life impact for people with BBS and their carers (see sections 3.19 to 3.21).

The committee considered whether any of these uncertainties were solely because of challenges with evidence generation caused by the rarity of BBS. It agreed that further data may help resolve the uncertainty about utilities and setmelanotide's treatment effect on BMI. But it noted that most of the uncertainties would remain if even more robust data was available from the trials. The committee considered this when deciding whether to apply the QALY weighting. It recalled that for a QALY weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. It agreed that there was evidence of significant QALY gains. But it considered they were associated with very high uncertainty about the robustness of the QALYs generated by the model, even when considering factors such as uncaptured benefits (see section 3.27). 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.

## Cost-effectiveness estimates

### Company and EAG cost-effectiveness estimates

3.25 The company's base case showed that setmelanotide was associated with an ICER of £169,658 per QALY gained compared with best supportive care. This was in a mixed population of children (60%) and adults (40%; see section 3.14), and assuming 84% of people with BBS would have severe hyperphagia and 16% moderate hyperphagia at baseline (section 3.15). In the EAG's base-case analyses that assumed a 75% to 25% split between severe and moderate hyperphagia at baseline, the ICER in the mixed population was £174,904 per QALY gained compared with best supportive care. The company also submitted an ICER in the population in which everyone entered the model as children and can continue setmelanotide into adulthood unless they stop because

of lack of effect (see section 3.18). In this, it included a 75% to 25% split between severe and moderate hyperphagia at baseline. The ICER was £171,844 per QALY gained compared with best supportive care. All reported ICERs include the confidential discount for setmelanotide available to the NHS updated by the company after the third committee meeting, and did not have a QALY weighting applied.

### Preferred assumptions and committee preferred ICER

3.26 Considering the company's and EAG's analyses, the committee's preferred assumptions included:

- using the mixed population (60% children and 40% adults)
- assuming a mixed baseline distribution of severe (75%) and moderate (25%) hyperphagia
- using the EAG's scenario in which people whose condition responded to setmelanotide but did not have a BMI-class drop moved from severe to moderate hyperphagia
- using the EAG's preferred treatment effect on BMI-Z score for children, which adjusted for a placebo effect
- using a 1% annual stopping rate
- using utility values for BMI or BMI-Z class health states from the literature
- applying the BBS multiplier calculated by the EAG using corrected mapping from the PedsQL scores in RM-493-023
- assuming 1 carer per adult with BBS
- assuming ongoing management of setmelanotide in local secondary care weight management clinics.

The committee noted that assuming a mixture of hyperphagia severities at baseline and a variable treatment effect on hyperphagia increased the ICER significantly. Using a 1% stopping rate had a minimal impact on costs but increased the undiscounted QALYs, meaning that a larger QALY weighting could be applied. The committee noted that the EAG's

base case at the third committee meeting included all of its preferred assumptions. So, its preferred ICER was £174,904 per QALY gained with no QALY weighting applied. The committee had agreed to apply a QALY weighting to account for the size of the incremental therapeutic improvement (section 3.24). But because of considerable uncertainty in QALYs generated in the model, it was appropriate to apply 90% of the weighting. When considering this, its preferred ICER using the mixed population of adults and children 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 and that this warranted consideration of the analyses in which everyone entered the model as children (see section 3.14). 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.

### Uncaptured benefits in the company's modelling

3.27 The company highlighted several uncaptured benefits in its modelling that meant the cost-effectiveness estimates were conservative, including that:

- people who stopped setmelanotide immediately reverted to their baseline hyperphagia status, whereas a tapering of benefit would be expected in clinical practice
- the model did not account for natural weight gain in people with BBS who did not have setmelanotide
- people with severe hyperphagia were likely to have a higher response rate to treatment than people with moderate hyperphagia
- no one was modelled to have no hyperphagia after treatment in the base case, which would be associated with a utility benefit
- because the upper BMI-Z class stopped at 4, the model did not capture comorbidity and mortality benefits for people with very high BMI or BMI-Z scores

- some obesity-related comorbidities (such as skin lesions) that can affect quality of life were not modelled
- data in the model was mostly from people of White ethnicity, which may under-represent some ethnic groups disproportionately affected by BBS.

The committee acknowledged that several benefits of setmelanotide may have been underestimated. It recalled the unmet need for successful treatments for BBS (see section 3.3). It also recalled that semaglutide, which may convey some benefit in combination with other weight loss treatments, is only licensed for 2 years of use. So, there are no effective long-term treatments available for BBS. The EAG acknowledged the company's arguments but noted that the model favoured setmelanotide in several aspects, including that:

- there was no waning of effect over time for setmelanotide modelled, which may have outweighed the effects of not including a tapering of benefit for people who stop setmelanotide
- there was no accounting for natural weight gain in people with BBS who did have setmelanotide, which may have cancelled out any weight gain in people having best supportive care.

The committee considered the company's and EAG's arguments. It could not be certain about the extent to which the model favoured setmelanotide or the comparator. The committee recalled the high level of uncertainty in the cost-effectiveness estimates for setmelanotide (see section 3.25). It agreed that it had updated its preferred assumptions on hyperphagia baseline distributions (see section 3.15) and setmelanotide's effect on hyperphagia (see section 3.17) to less conservative approaches after the second committee meeting. When weighing up the flexibility already applied against any uncaptured benefits, the committee considered that setmelanotide could not be considered cost effective in the mixed population of adults and children. So, it could only recommend

setmelanotide for routine commissioning in people who start setmelanotide between age 6 and 17.

## Managed access

### Recommendation with managed access

3.28 Having concluded that setmelanotide could not be recommended for routine use in people who start treatment as adults, the committee then considered whether it could be recommended with managed access for treating BBS in this population. It noted that the company had not submitted a managed access proposal, so it could not make a recommendation for managed access at this stage.

## Other factors

### Equality

3.29 The committee noted that the population for which setmelanotide is indicated includes children and young people. It further noted the additional benefits beyond health that the treatment may have for children and young people 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 committee acknowledged and considered the nature of the population as part of its decision making. It agreed that its recommendation had addressed this issue. 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, the company highlighted 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 recommendation applies equally, regardless of ethnicity, so a difference in condition prevalence does not in itself represent an equality issue. It concluded that all equalities issues for setmelanotide had been considered in its decision making.

## Innovation

3.30 The committee considered whether setmelanotide was innovative. The clinical experts stated that type 2 diabetes can often affect vision and kidney function. So, by improving obesity-related comorbidities, setmelanotide had the potential to indirectly affect the progression of comorbidities not linked to BMI. The committee noted that the utility decrement for non-obesity-related comorbidities applied equally to people whose condition did and did not respond to setmelanotide (see section 3.20). It also recalled the unmet need for BBS and that setmelanotide is the first treatment to address the underlying hyperphagia

(see section 3.1). The committee concluded that setmelanotide may be innovative.

### Conclusion

#### Recommendation

3.31 The committee noted that its preferred ICER in the mixed population of adults and children was above the threshold normally considered an acceptable use of NHS resources in a highly specialised technology when applying a QALY weighting (see section 3.25). It recalled that several of the company's assumptions were conservative. But some benefits may also have been overestimated by the model, so the size of any uncaptured benefits was unknown and no further flexibilities were needed (see section 3.27). But, the committee considered that 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 who start treatment aged between 6 and 17 years (with continuation into adulthood if clinically indicated).

## 4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a

drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has BBS and the doctor responsible for their care thinks that setmelanotide is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 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

**Peter Jackson**

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 and a project manager.

**Emma Douch**

Technical lead

**Rufaro Kausi and Ewa Rupniewska**

Technical advisers

**Celia Mayers and Daniel Davies**

Project managers

ISBN: [to be added at publication]