Highly Specialised Technology

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

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Contents:

The following documents are made available to stakeholders:

Evaluation committee meeting 2 documents:

1. **Draft Guidance Document (DG)** as issued to consultees and commentators

2. **Comments on the Draft Guidance from** Rhythm Pharmaceuticals:
   a. Response form
   b. Appendix A – vignette study definitions
   c. Appendix B – Early onset of obesity model technical report
   d. Appendix C – shift in BMI-Z class analysis (placebo corrected)
   e. Revised cost-effectiveness results
   f. Caregiver burden in Bardet-Biedl syndrome: findings from the CARE-BBS study, Forsythe et al

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. Bardet-Biedl Syndrome UK (BBS UK)
   b. British Obesity & Metabolic Surgery Society

There were no comments received on the Draft Guidance through the NICE website.

4. **External Assessment Group critique of company response to the DG**

Evaluation committee meeting 3 documents:

5. **External Assessment Group analysis conducted post-evaluation committee meeting 2 (ECM2)** produced by Bristol-TAG

6. **Company rationale regarding potential inaccuracies**

7. **External Assessment Group response to company rationale regarding potential inaccuracies** produced by Bristol-TAG

8. **Clinical expert responses to queries from NICE technical team on BMI-z shift:**
   a. Elizabeth Forsythe, Consultant in Clinical Genetics – clinical

expert, nominated by Rhythm Pharmaceuticals

b. Dimitri Pournaras, Consultant Bariatric and Metabolic Surgeon – clinical expert, nominated by British Obesity & Metabolic Surgery Society

9. External Assessment Group response to clinical expert comments on BMI-z shift produced by Bristol-TAG:

a. Response

b. Additional scenario

10. Company post-ECM2 submission

11. External Assessment Group critique of company post-ECM2 submission produced by Bristol-TAG:

a. Main critique

b. EAG new analyses with 90% QALY weighting – requested by evaluation committee

12. External Assessment Group additional analyses post-ECM3 produced by Bristol-TAG

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

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: August 2023

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: 24 August 2023
- Second evaluation committee meeting: 14 September 2023
- Details of the evaluation committee are given in section 4

Issue date: August 2023

1 Recommendations

1.1 Setmelanotide is not recommended, within its marketing authorisation, for treating obesity and hyperphagia in genetically confirmed Bardet-Biedl syndrome (BBS) in people aged 6 years and over.

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 early onset severe obesity and hyperphagia (characterised by a feeling similar to starvation), 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. They 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.

In addition to the uncertainties in the clinical evidence, there are issues with the economic model. These include assumptions:

- that everyone has severe hyperphagia when they enter the model
- about setmelanotide's effect on BMI-Z in people aged under 18 years
- that all people whose condition responds to setmelanotide have mild hyperphagia
- on the quality-of-life values related to BMI

- about the effect on quality of life of BBS comorbidities not related to obesity
- on what the quality-of-life benefits are for carers of people whose condition responds to treatment.

This means that it is not possible to determine the most likely cost-effectiveness estimates. So, setmelanotide cannot be recommended and more data is needed.

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)…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.

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. This makes setmelanotide available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 severe, early onset obesity and hyperphagia. BBS is likely associated with increased death rates compared with general obesity because of renal failure and early onset of comorbidities related to severe obesity in childhood, such as diabetes and cardiovascular conditions. But this is uncertain. 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 exercise 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 level of obesity, resulting lack of mobility and strain on the body. 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. 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. One expert estimated that, in their experience, around 50% to 60% of people with BBS have severe hyperphagia in clinical practice. The committee considered the definitions of severe, moderate, and mild hyperphagia that had been provided by the company as part of a vignette to collect utility data (see section 3.18). But it noted some crossover between the description of activities associated with severe hyperphagia provided by the clinical experts at the meeting and the vignette definition of moderate hyperphagia. The committee was concerned that it is likely that some people with moderate hyperphagia will have setmelanotide in clinical practice. It thought this because there is no standardised severity scale, and identification relies on clinical judgement. They also recalled 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, and
- whether it would be possible to identify these people in clinical practice.

So, it considered that the whole population in the marketing authorisation would likely be offered setmelanotide.

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 (results assessed after 52 weeks for people randomised to setmelanotide; after 66 weeks for people randomised to placebo).

  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 was the first 32 people enrolled in the study and informed the analyses at 52 weeks.
- The supplemental cohort included a further 12 patients, 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 suggestive of 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 may improve 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. It concluded that setmelanotide may improve hunger in and the quality of life of people with BBS in the short term, but the results are 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 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. The EAG stated that the treatment effect from the placebo arm between week 14 (when people swapped to setmelanotide) and week 24 (when people could enter the open-label extension study) would give an estimate of the

treatment effect accounting for any regression to the mean. The committee concluded that there was potential bias from a lack of randomised controlled data at week 52. It agreed that the effect of potential regression to the mean should be further explored, with 52-week outcomes (hunger score, BMI and BMI-Z) from the trial adjusted as appropriate.

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). While the company's response rates used data from week 52 of RM-493-023, it was uncertain as to when response to setmelanotide would be assessed in clinical practice. It concluded that behavioural changes are important markers of response to treatment. It also concluded that the criteria and timepoint for assessing response in clinical practice may differ from those used in the clinical trials.

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, 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 in which all people entered the model as adults and a mixed population in which 60% of the modelled population entered the model at age 6 years and 40% at age 18 years. The clinical experts stated that the company's mixed population may have overestimated the proportion of children with BBS in current clinical practice. But the company highlighted that, in future, it expected setmelanotide to be started when BBS is diagnosed, which would more likely be in childhood. The committee considered it preferable to use the scenario that best represented current clinical practice, while noting the uncertainty in the distribution of adults and children. So, it preferred the mixed population for decision making, but considered analyses in which people entered the model as children.

Baseline hyperphagia status

3.15 The company assumed that all people with BBS had severe hyperphagia at baseline, in line with its updated population (see section 3.5). The EAG provided a scenario in which, at baseline, 60% of people had severe hyperphagia and 40% had moderate hyperphagia. This was based on the proportion of people with severe hyperphagia in clinical practice estimated by the company's clinical experts. The committee recalled the challenges of differentiating between moderate and severe hyperphagia and its conclusion that some people with moderate hyperphagia would likely have setmelanotide in clinical practice (see section 3.5). It also recalled that a mixture of hyperphagia severities was likely included in the trial population (see section 3.7). It agreed that the modelled population should reflect setmelanotide's use in clinical practice. So, it preferred the EAG's scenario assuming a mixture of moderate and severe hyperphagia at baseline for decision making.

Modelling treatment effect on hyperphagia

3.16 At 14 weeks, the company assumed that all people whose condition responded to setmelanotide transitioned to mild hyperphagia independent of change in BMI-Z or BMI. This 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 committee understood from the patient and clinical experts that hyperphagia is much more than hunger. So, it was concerned that the improvements in hyperphagia included in the model were based on assumptions alone, so making a large contribution to improvement in quality of life highly uncertain. 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. Based on other weight loss interventions, they thought it likely that there would be varying degrees of response to treatment. 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, the EAG modelled people with severe hyperphagia at baseline moving to both moderate and mild hyperphagia. Transitions were informed by 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). The committee agreed that there was substantial uncertainty about the treatment effect on hyperphagia. While acknowledging the uncertain correlation between BMI and hyperphagia (see section 3.12), it preferred the EAG's scenario, which was based on trial data instead of assumptions. The committee also recalled its preference for a distribution of severe and moderate hyperphagia at baseline (see section 3.15). The EAG explained that the

model would not allow a variable treatment effect as well as a mixture of hyperphagia severities at baseline. The committee acknowledged that this was an important limitation of the modelling. It considered that people with moderate hyperphagia at baseline would have a smaller treatment response when moving to mild hyperphagia than people who started with severe hyperphagia. So, it thought that some variation in treatment effect would already be captured. Because of the modelling limitations, the committee only accepted the company's approach when combined with a mixed hyperphagia severity distribution at baseline.

Modelling treatment effect on BMI-Z in children

3.17 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, with the most frequently seen class shifts applied to people whose condition responded to treatment.

The EAG noted that children and young adults 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. Based on this, in its base case, the EAG used a lower reduction in classes for children, equal to that in adults. The company highlighted that its chosen BMI-Z class cut offs had larger intervals at the extremities (less than 2 and over 4) than those used in the middle.

This may have underestimated the number of class changes in people with a baseline BMI-Z score of over 4. Also, RM-493-023 did not allow dietary and exercise modifications, which would likely be used in combination with setmelanotide in clinical practice and may convey some benefit. But the committee noted that a little over half the children in RM-493-023 had the modelled class reduction, with most others having a lower response. It recalled that the treatment effect reported in the trial may have been overestimated because of potential regression to the mean (see section 3.10). It also had concerns about using the BMI shift data in the model. It acknowledged the company had chosen the BMI class cut offs based on the available comorbidity data. But it noted that, by using this approach, the model had not captured the variability seen in the clinical trial for BMI-Z score changes. It would have preferred to see analyses that either applied the mean BMI-Z score shift (instead of the most frequent) or the actual BMI-Z score shift from individual trial participants to the baseline BMI-Z proportions. The committee concluded that the company's modelling of treatment effect on BMI-Z added uncertainty. It acknowledged the lack of alternative approaches and the variability in the results for children. But it preferred the conservative BMI-Z score shift used in the EAG base case 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 more than 1% of people had stopped setmelanotide in RM-493-023 because of a lack of effect

(exact rates and confidential and cannot be reported here). So, it stated that the long-term stopping rates may be higher in clinical practice and included a stopping rate of 2% in its base case. The clinical experts explained that, based on their experience with glucagon-like peptide-1 receptor agonists such as semaglutide, some waning of treatment effect could be expected over time. But, without treatment, people with BBS steadily gain weight, so even a plateau of weight loss is beneficial. The ongoing treatment effect for setmelanotide is uncertain because it is a new class of drug with little available long-term data. High adherence to treatment is expected because reducing hyperphagia has a big quality-of-life benefit. But the need to self-inject every day may mean some people whose condition responds to treatment may stop setmelanotide. The committee recalled that the criteria for stopping treatment in the clinical trial may have differed from those used in clinical practice (see section 3.12). But, acknowledging the short follow up in the trials, it agreed that this should be informed by clinical data when possible. It concluded that the EAG's stopping rate of 2% should be used in decision making as a proxy for treatment waning.

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 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) from a vignette 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. It preferred to use Forsythe et al. because it 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. The EAG suspected that this error likely applied to those values mapped from Riazi et al. in the company's base case as well. The EAG corrected the company's mapping from trial PedsQL values, which it preferred for its base case. The committee noted that the data from Riazi et al. was 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. The committee acknowledged that NICE's health technology evaluations: the manual specifies a preference for using trial-based utilities where available. But, given the uncertainty introduced by the small sample size from the trial available for mapping, the committee agreed that this constituted an exceptional circumstance. It concluded that utilities from the literature were most appropriate for decision making. But it agreed that the error in the company's mapping should be corrected.

BBS utility multiplier

3.20 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 assumption instead of clinical evidence. The committee recalled its preference to use literature-based values from general obesity for baseline BMI health state utilities (see 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 scenario 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. It assumed an average 1.5 carers per child or young person with BBS. For adults, the number of carers was based on a survey by Bardet-Biedl Syndrome UK, which captured care for 121 adults with BBS. The EAG agreed it was appropriate to include a carer disutility. It also agreed that a lower care burden for adults was expected because carers generally have less control over diet and lifestyle at this point. It noted that the company had not provided the results of the BBS UK survey for verification, but used the estimate in its base case. The

committee agreed that a carer disutility was appropriate because of the high quality-of life-burden for carers of people with BBS (see section 3.2). But it was concerned that the company's carer disutility was applied at equal rates to carers of people having both setmelanotide and best supportive care. The patient experts explained that controlling diet and food-seeking behaviours constitutes a large proportion of the care needed for people with BBS. So, setmelanotide would likely improve quality of life for carers when hyperphagia was reduced in the person with BBS. The committee concluded that a quality-of-life benefit should be modelled for carers of people whose condition responds to treatment.

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. The committee concluded that ongoing monitoring for setmelanotide would likely take place in local tier 3 obesity clinics in secondary care. It concluded that the cost of additional visits should be included in the model.

Quality-adjusted life year (QALY) weighting

Criteria for applying a QALY weighting

3.23 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. So, it concluded that some of the criteria for applying a QALY weighting were likely met. It considered this in its decision making. But there were considerable uncertainties (see section 3.26) in the QALY gain estimates, so the committee was unable to conclude on the exact QALY weight to apply without further information.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.24 The company's base case showed that setmelanotide was associated with an ICER of £197,641 per QALY gained compared with best supportive care in the paediatric population. Considering a mixed population of children (60%) and adults (40%) increased the ICER to £204,894. When assuming all people enter the model as adults, the ICER was £229,614. These ICERs included the confidential discount for setmelanotide available to the NHS. In the EAG's base-case analyses, setmelanotide was associated with an ICER compared with best supportive care of:

- £203,784 per QALY gained in children
- £208,457 per QALY gained in the mixed population

- £222,857 per QALY gained in adults.

Acceptable ICER

3.25 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 and moderate hyperphagia
- using the EAG's preferred treatment effect on BMI-Z score for children (while acknowledging the uncertainty)
- using a 2% 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-49--023
- assuming ongoing management of setmelanotide in local secondary care weight management clinics.

The committee noted that it had not been presented with an ICER that included all of its preferred assumptions. It noted that using BMI-Z health state utilities from the literature and assuming a mix of hyperphagia severities at baseline significantly increased the ICER. So, when using its preferred assumptions, the ICER was likely to be over the cost-effectiveness threshold, even when considering a QALY weighting.

Uncertainties to explore further in the modelling

3.26 The committee recalled the high level of uncertainty surrounding some of the company's assumptions. It noted the company should explore the following in the modelling:

- a reduction in carer disutility in people whose condition responds to setmelanotide

- corrected mapping of BMI-Z health state utilities from the literature
- alternative ways to model treatment effect on BMI-Z, such as applying the mean BMI-Z score shift (instead of the most frequent) or the actual BMI-Z score shift from people in the trial to the baseline BMI-Z proportions
- amendments to the model to allow a variable treatment effect on hyperphagia, as well as a mixture of hyperphagia severities at baseline
- the effect of potential regression to the mean for the 52-week outcomes (hunger score, BMI and BMI-Z) and adjusting for this as appropriate.

Managed access

Recommendation with managed access

3.27 Having concluded that setmelanotide could not be recommended for routine use, the committee then considered whether it could be recommended with managed access for treating BBS. 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

3.28 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. 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. The committee considered that its recommendation applies to the full licensed population, and it could not make a recommendation outside of this. It concluded that all equalities issues for setmelanotide had been considered in decision making.

Innovation

3.29 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

3.30 The committee noted that it had not been presented with an ICER that included all of its preferred assumptions (see section 3.25). But it concluded that the ICER was likely to be above the threshold normally

considered an effective use of NHS resources in a highly specialised technology. So, it could not recommend setmelanotide for routine commissioning to treat obesity and hyperphagia in BBS. The committee concluded that the company and stakeholders should provide additional information for consideration at the next evaluation committee meeting (see section 3.25 and section 3.26).

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

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

Technical adviser

Celia Mayers and Daniel Davies

Project managers

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 24 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Rhythm Pharmaceuticals

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the evaluation stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	We, Rhythm Pharmaceuticals do not have past or current, direct or indirect links to, or funding from, the tobacco industry
Name of commentator person completing form:	Nicolas Touchot

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Introduction and update to PAS:** Rhythm would like to thank the HST evaluation committee for their appraisal of the setmelanotide submission and the EAG and NICE team for providing additional

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	clarification on the draft guidance. As will be demonstrated in our response, Rhythm has carefully considered the committees preferences. We have provided additional clarifications where necessary, made changes to the base-case approach aligned with committee preferences and provided further scenario analyses to support committee decision making. In addition to these changes, Rhythm has updated its simple discount patient access scheme to [redacted] We hope that these changes demonstrate our commitment to making setmelanotide available to patients.
2	**Draft guidance section 3.15 [updated base-case approach to baseline populations]** Rhythm recognises the committee preference to consider a mixture of both moderate and severe hyperphagia at baseline for decision making and have therefore updated the company base-case to reflect this. The draft guidance refers to the split of severe and moderate hyperphagia in BBS patients with obesity in clinical practice to be 60% severe and 40% moderate. Whilst Rhythm accepts that this is the split of patients in clinical practice, it is important to recall that the mechanism of setmelanotide works through restoring activity to the MC4R pathway (responsible for controlling feelings of hunger and satiety). Because severe hyperphagia is caused by impairment of the MC4R pathway (leading to overwhelming, heightened, and relentless hunger), Rhythm anticipates that patients with severe hyperphagia will be prioritized for treatment with setmelanotide due to both higher burden of disease and to higher likelihood of response, thus enriching the treated population with patients experiencing severe hyperphagia. Because of this enrichment, it is anticipated that the majority of patients-initiated treatment with setmelanotide in clinical practice will have severe hyperphagia at baseline. To reflect this, the base-case has been updated to 75% severe hyperphagia and 25% moderate hyperphagia at baseline. It should be noted that Rhythm considers this to be a conservative approach. Due to the mechanism of action, we also expect response rate (change in hyperphagia leading to change in eating habits leading to significant weight reduction) to be higher in patients with severe hyperphagia. In clinical practice, this would lead to a further enrichment of patients with severe hyperphagia at baseline continuing therapy long term beyond the initial 14 weeks period. This additional enrichment is not reflected in the base-case.
3	**Draft guidance section: 3.5 and 3.15 [clarification on severe vs. moderate definitions]** Whilst Rhythm has updated the base-case to reflect the committee preference, we also retain the opinion that moderate and severe patients are distinguishable in clinical practice and would like to take this opportunity to provide additional clarification the committee. **Diagnosis by multidisciplinary teams with expertise in BBS**. BBS patients with severe hyperphagia will be diagnosed and initiated on treatment by clinical experts in one

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	of the four centres of excellence for the management of BBS. As mentioned by the patient expert during the meeting and explained in the clinical expert submissions, a multidisciplinary team including clinicians, psychologists and nutritionists contributes to the diagnostic process. Similar to the situation described in HST21, the diagnosis of severe hyperphagia in BBS will not be reliant on the opinion of one individual. In addition, as treatment would be restricted to specialist centres of excellence, diagnosis and treatment initiation would be by clinicians with expertise in differentiating levels of severity. **Differences in severe and moderate hyperphagia.** The draft guidance suggests that there is overlap between definitions of moderate to severe disease. Rhythm would like to clarify that there are clear differences in the frequency and intensity of the indicators for moderate and severe hyperphagia, as described in the vignette study (please note, due to formatting constraints the table of definitions has been provided as an appendix). For example, eating 'a large number of calories when you wake up during the night' (discussed during the appraisal committee meeting), occurs 'almost every night' in the definition of severe hyperphagia, compared with moderate hyperphagia where it occurs 'about 2-3 times per week'). Clinicians within the specialist centres will have the experience and ability to clearly distinguish between moderate and severe hyperphagia populations (as defined in Appendix Document A). During the appraisal committee meeting, clinical experts indicated that BBS patients with severe hyperphagia would be identifiable by a person's weight, and by maladaptive and extreme food-seeking behaviour (as explained in the draft guidance). In addition to this, clinical experts during the appraisal committee meeting suggested that lack of an assessment tool for severe hyperphagia is because these patients can easily be identified by clinicians within the specialist centres, resulting in a lack of need for additional tools.
4	**Draft guidance section 3.15 [amendments to the model for variable treatment effect]** The draft guidance states that the model "would not allow a variable treatment effect as well as a mixture of hyperphagia severities at baseline" and that "the committee acknowledged that this was an important limitation of the model". We would like to clarify that the model does allow both parameters to be changed at the same time. Whilst each of these parameters pulls into a single set of utility multipliers, both parameters can be changed in parallel. This can be done in the "calculations" tab of the model under the "hyperphagia utility multipliers" table. Rhythm would be happy to demonstrate and discuss this with the EAG if that would be considered helpful. To explore a variable treatment effect as well as a mixture of hyperphagia severities at baseline, Rhythm has conducted a two-way threshold analysis with the parameters outlined in Table 1.

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<table>
<tr><td></td><td>

Table 1 Overview of two-way threshold approach

<table>
<tr><th>Parameter</th><th>Threshold analyses explored</th></tr>
<tr><td rowspan="3">Hyperphagia at baseline</td><td>100% severe</td></tr>
<tr><td>75% severe, 25% moderate (base-case)</td></tr>
<tr><td>60% severe, 40% moderate</td></tr>
<tr><td rowspan="3">Treatment effect</td><td>100% Severe to No Hyperphagia; 100% Moderate to No Hyperphagia (three-class shift for severe, two-class shift for moderate)</td></tr>
<tr><td>100% Severe to Mild; 100% Moderate to No Hyperphagia
(two-class shift for both severe and moderate)</td></tr>
<tr><td>100% Severe to Mild; 100% Moderate to Mild (two-class shift for severe, one-class shift for moderate) (base-case)</td></tr>
</table>

</td></tr>
<tr><td>5</td><td>

Draft guidance section: 3.14 [key issue: mixed vs. paediatric population for treatment initiation]

Rhythm reiterates the appropriateness of only reflecting treatment initiation within children alone. While most patients with BBS have normal birth weight, by 2 years of age it is estimated that >55% of children with BBS are overweight or obese and by the age of 5 years obesity rates exceed 90% (Pomeroy 2021). Overall, weight gain is considered to be so dramatic that most people will receive a diagnosis in early childhood. In addition, screening and genetic testing for BBS is expanding and this will promote early BBS diagnosis and consequently, treatment initiation.

We would also like to draw the committee's attention to HST21, where the committee recognised that "severe obesity usually presents within the first few years of life and the move towards earlier diagnostic testing".

It is also important to reiterate that early treatment is important to reduce and prevent long-term consequences of childhood obesity on other aspects of health and on mental well-being (including but not limited to risk of metabolism syndrome, CVD and type 2 diabetes mellitus (Haqq et al. 2023 TOS and ESPE abstracts)). Because of this, treatment will begin soon after diagnosis.

In addition to consideration of HST21 discussed above, Rhythm also notes that there is previous precedent to support the use of treatment initiation in a manner that reflects expected anticipated earlier identification in other HST topics as well. For instance, in HST26, the committee accepted the company's base-case of treatment initiation at 4-years – this was based on anticipated earlier identification, diagnosis and treatment and preferred over the EAGs preference of treatment initiation (which reflected current practice).

</td></tr>
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Draft guidance sections: 3.17 [BMI-Z shift]

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	The draft guidance requested that the company explore alternative ways to model treatment effect on BMI-Z. As acknowledged in the committee meeting slides and the EAG's critique of the technical engagement response, the true mean class reduction is likely to be between a [redacted] and [redacted] class change. Rhythm considers that a [redacted] class reduction in BMI-Z is an underestimation of the effect on BMI-Z (as described in the response to technical engagement). In addition, the mean difference in BMI-Z score from baseline is [redacted]. This corresponds to an [redacted] average class change ([redacted]/0.5). Rhythm considers this a more accurate representation of the effect of setmelanotide. *[Rhythm notes that previous documents including the technical engagement response refers to a [redacted] class shift; this has been checked and has been recognised as a rounding error, hence [redacted] has been used instead].* Rhythm acknowledges that the model is limited in its ability to reflect variable treatment effects and the committees request to explore alternative ways to model treatment effect on BMI-Z. To meet the committee's requirements and to reflect the [redacted] class change in the cost-effectiveness results, Rhythm has used a weighted average of ICERs for [redacted]-level and [redacted]-level shifts. This means that the updated base-case ICER is calculated by: • Recording the model results using [redacted] BMI-Z shift and recording the results using [redacted] BMI-Z shift • Applying a weighted average to the cost-effectiveness results (i.e., [redacted]% using the [redacted]-class shift) Within the draft guidance, it is recognised that the EAG's base-case preferred by the committee is conservative. The committee also noted that it would have preferred to see analyses that applied the mean BMI-Z score shift. Rhythm considers that its updated approach of using a weighted average is a more appropriate reflection of the true benefit of setmelanotide and is better aligned with the committee's preference of using the true BMI-Z shift. Rhythm notes the committee had also requested exploration of the impact of a potential placebo effect. The placebo effect in BMI-Z is small (estimated 2.5% reduction) and has a small resulting impact on the BMI-Z shift. Correcting BMI-Z for the placebo effect: • Does not lead to a change in shift in BMI-Z class for any patients • Based on classes being defined by increments in 0.5 BMI-Z scores, does not change the mean shift in BMI-Z classes from [redacted] • Reduces the mean difference in BMI-Z score to [redacted] which is [redacted] Based on this, Rhythm has also submitted a scenario analysis to reflect a weighted average class change of [redacted]. This scenario has been included for completeness, however, is considered a conservative approach that underestimates the impact of setmelanotide on BMI-Z class changes.

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7	**Draft guidance section: 3.18 [discontinuation: 1% vs. 2%)** Rhythm acknowledges that within the draft guidance the committee has indicated a preference of a 2% discontinuation rate. The draft guidance suggests that this approach is a better reflection of the clinical trial. However, Rhythm considers this to be a misunderstanding of the data requiring further clarification. Rhythm appreciates that NICE and EAG enabled the opportunity for this to be further explained on Wednesday 16th August. The points raised during this call are further explained below and provide the rationale of our position of retaining a 1% discontinuation rate. 1. The draft guidance notes that the EAG "was concerned that more than 1% of people had stopped setmelanotide in RM-493-023 because of a lack of effect". It should be highlighted that the EAGs preference is based on data including [redacted] patients discontinuing due to adverse events and [redacted] patient discontinuing due to a lack of efficacy. The EAG acknowledge that discontinuation due to adverse events may occur soon after treatment is initiated, and/or be managed using dose titration [EAG report, section 4.2.6.4]. In addition, the [redacted] patient discontinuing due to a lack of efficacy (patient 013-003), discontinued early in the trial at day 255. Considering the lack of weight loss observed by this patient, this patient is classified as a non-responder in the study (Table 2). It should also be noted that this patient also demonstrated no change in hunger (Table 3). Both of these sets of results (a lack of weight change and a lack of change in hunger) are clear signs that there is no change in hyperphagia and would clearly signal to clinicians that the patient is a non-responder and for treatment to be stopped early. It is important to note that the model takes a response-based approach and within this framework, patient 013-003 is classified as a non-responder within the response rate. Because of this, if this patient were to be considered when developing a discontinuation rate (i.e., as is the case in the EAGs base-case approach), this would result in double-counting. Rhythm strongly considers this an inappropriate approach and so has retained the original base-case approach of a 1% discontinuation rate. We have also provided a 2% discontinuation rate scenario analysis for the committee's consideration. *Table 2 BMI efficacy data profile: patient 013-003* **Study day / visit** | **Current dose (mg)** | **Weight (kg)** | **Height (cm)** Day -11 / visit 1 | [redacted] | [redacted] | [redacted] Day 1 / visit 2 | [redacted] | [redacted] | [redacted] Day 22 / visit 3 | [redacted] | [redacted] | [redacted] Day 50 / visit 4 | [redacted] | [redacted] | [redacted] Day 78 / visit 5 | [redacted] | [redacted] | [redacted] Day 117 / visit 6 | [redacted] | [redacted] | [redacted]

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Table 3 Weekly average of the daily hunger score: patient 013-003

Study week / visit	Worst hunger score	Morning hunger score	Average hunger score
-1 / visit 1	[redacted]	[redacted]	[redacted]
1 / visit 2	[redacted]	[redacted]	[redacted]
2 / visit 3	[redacted]	[redacted]	[redacted]
6 / visit 5	[redacted]	[redacted]	[redacted]
10 / visit 6	[redacted]	[redacted]	[redacted]
14 / visit 7	[redacted]	[redacted]	[redacted]

2. Rhythm would also like to stress that clinical data demonstrates that non-responders would be very easily identified at an early stage in clinical practice and it is therefore inappropriate to incorporate a non-responder in yearly discontinuation. Figure 1 demonstrates:

    - A marked decrease in hunger scores by week 14 – demonstrating that patients having setmelanotide can be identified early.

    - A marked increase in hunger scores during the re-titration phase (needed to maintain blinding after 14 weeks) in the setmelanotide arm. This notable increase in hunger during a re-titration phase reinforces Rhythm's position that stopping treatment would lead to a noticeable increase in hunger and hyperphagia. This noticeable impact would be a reminder to take setmelanotide and would lead to adherence of treatment. In fact, the committee itself has acknowledged within the Draft guidance that "high adherence to treatment is expected". In addition, during the appraisal committee meeting, clinical experts noted that the main stopping criterion would be a change in eating behaviour and further explained that this would be apparent very early on after treatment initiation.

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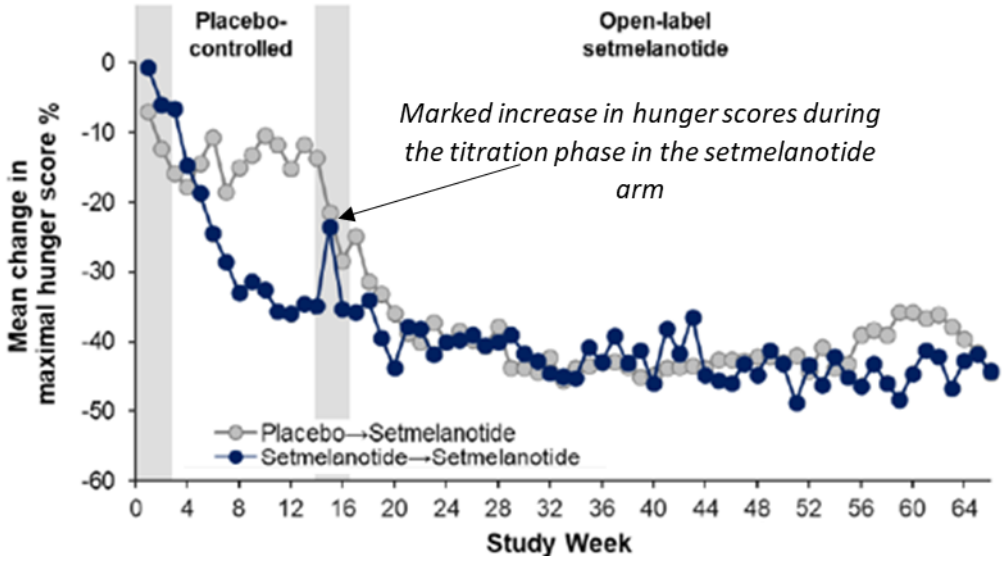
Figure 1 Mean change in maximal hunger score in patients aged ≥12 years without cognitive impairment (Study RM 493 023, pivotal patients with BBS)



3. The committee notes within the draft guidance that "the need to self-inject every day may mean some people whose condition responds to treatment may stop setmelanotide". This was also recognised within the previous setmelanotide appraisal (HST21). To reflect this, in HST21, the EAG suggested a discontinuation rate of 1%. This was considered appropriate by clinical advisors and accepted by the committee. Considering that the committee acknowledges adherence is likely to be high, and that discontinuation is expected to be for similar reasons to HST21, Rhythm strongly considers it inappropriate to suggest that a higher discontinuation rate of 2% is suitable for this appraisal.

4. The draft guidance also states that "The clinical experts explained that, based on their experience with glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide, some waning of treatment effect could be expected over time." In addition, the committee concludes that the 2% discontinuation should be used as a "proxy of treatment waning". Firstly, Rhythm would like to stress that there are clear and important differences in the mechanism of action between GLP-1 agonists and setmelanotide. There is no basis to assume waning of setmelanotide based on waning seen with semaglutide. Unlike GLP-1 agonists, setmelanotide activates melanocortin receptors in the brain to restore the MC4R pathway signalling to reduce hyperphagia. Because of this, setmelanotide is expected to have negligible treatment waning. There is a lack of rationale to assume waning with setmelanotide and it is

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	important to also recall that the committee did not consider there to be a need to reflect waning with setmelanotide in HST21. 5. Rhythm also finds it important to consider the conservative nature of the model. People who discontinued treatment in both arms are modelled with their BMI/BMZ category and hyperphagia levels returning to baseline without any tapering. This means that the gradual tapering of treatment effect that people will receive is not captured.
8	**Draft guidance section 3.21 [carer disutility]** The committee held concern regarding the application of carer disutility in the model, requesting that "quality of life benefit should be modelled for carers of people whose condition responds to treatment". We welcome the opportunity to clarify that the current model does consider the influence of treatment response to caregiver disutility associated with the patients' hyperphagia with this hyperphagia-related carer burden being eliminated for patients responding to treatment. This benefit is lost (i.e., the disutility returns for the carer) when patients discontinue treatment, and carer disutility remains for best supportive care patients or setmelanotide patients deemed to be "non-responders". It should also be noted that the carer disutility used in the model only captures the impact of hyperphagia and weight gain and not the impact of other evolving BBS symptoms.
9	**Draft guidance section 3.21 [updated base-case approach to caregivers for adults]** Rhythm has updated the base-case assumptions to [redacted] caregivers for adults. This has been updated based on: • Recognition that the clinical expert submissions as part of the evaluation process indicate that there are "usually 1 or 2" carers for adults with BBS. This is reflected both in written submissions and the appraisal committee meeting slides (slide 37). • Acknowledgement that in current clinical practice, with best supportive care, patients with moderate hypergraphia may require fewer carers compared with the number of carers for patients with severe disease. Considering these points, Rhythm has assumed that with best support care, there will be [redacted] caregivers for adults with moderate hyperphagia (aligned with previous base-case) and 1.5 caregivers for adults with severe hyperphagia (a conservative approach taken in response to clinical expert opinion).
10	**Draft guidance sections 3.8, 3.9 and 3.11 [response to comments on uncertainty of treatment effect]** Rhythm was disappointed that the effectiveness of setmelanotide was not fully recognised within the draft guidance. In particular, the draft guidance states "setmelanotide ***may*** improve obesity-related outcomes in the short term" and "***may*** improve hunger and in the quality of life of people with BBS". Rhythm does not consider these statements to be an accurate reflection of the demonstrated benefits of setmelanotide. We would like to refer the committee to clinical

expert insights and recent additional analyses which (in addition to the data previously seen by the committee) that demonstrate the important benefits of setmelanotide.

1. Analysis on impact of setmelanotide on future metabolic syndrome risk in paediatric patients with BBS (Haqq et al. 2023 TOS and ESPE abstracts).

This analysis of metabolic outcomes in the Phase 3 RM-493 study evaluated the effect 1 year of setmelanotide using a metabolic syndrome score (MetS-Z-BMI), a measure where high scores indicate increased long-term risk of metabolic syndrome comorbidities. A 1.0-point increase in MetS-Z-BMI score in childhood increases the odds of future cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) by [redacted] and [redacted], respectively.

Table 4 demonstrates that paediatric patients with clinically meaningful weight reduction (defined as ≥0.3-point BMI Z score reduction) had a reduction in mean [SD] MetS-Z BMI score after 52-weeks of setmelanotide treatment of [redacted]. In contrast, paediatric patients without a weight response had an increase in mean [SD] MetS-Z BMI score [redacted]. The between group difference was [redacted].

Additionally, analysis in the overall population (paediatric and adult patients) demonstrates that patients who achieved a meaningful response of ≥10% weight loss (if ≥18 years old) or ≥0.3-point BMI Z score reduction (if <18 years old), had a reduced mean [SD] MetS-Z BMI score of [redacted]. In contrast, patients who do not meet weight thresholds saw an increase in mean [SD] MetS-Z BMI scores of [redacted]. The between group difference was [redacted].

Overall, these results show that setmelanotide treatment response is associated with reductions in metabolic syndrome severity score in patients with BBS, which are associated with reduced risk of metabolic syndrome, CVD, and T2DM. These data support the broad benefits of setmelanotide beyond weight loss and hunger reduction, thus supporting early initiation of treatment for potentially reducing future risk of CVD and T2DM.

Table 4 Mean change in MetS-Z BMI scores after 52-week setmelanotide treatment in paediatric and overall populations

Population	N	Mean change in MetS-Z-BMI score after 52 weeks of treatment [SD]
Paediatric with clinically meaningful weight reduction	[redacted]	[redacted]
Paediatric without weight response	[redacted]	[redacted]
Overall population (responders)	[redacted]	[redacted]
Overall population (non-responders)	[redacted]	[redacted]

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	2. Updated obesity comorbidity data (EOObesity-model) Estimating the consequences of obesity is a deeply intricate task that encompasses a broad spectrum of individual, health, economic, social, and methodological considerations. Rhythm has commissioned Stradoo, a specialised health analytics company to build a comprehensive model to estimate the effect of obesity on comorbidities and mortality risk – a full report on this model has been included in this response as an addendum. The model shows that the impact of early onset obesity on mortality and morbidities is markedly higher than what is currently represented in the base-case model. This is clearly demonstrated by the case example in the EOObesity technical report, which developed pathways for a modelled patient with a BMI-Z score of 2.5 at 2 years of age and a BMI-Z score of 4.0 at 4 years of age (i.e., reflecting early onset obesity). The modelling demonstrated that early paediatric treatment initiation and resultant weight loss at 6 years by two BMI-Z classes, led to a gain in life years of [redacted] years and a reduction of [redacted] DALYs. Treatment initiation and weight loss at an older age resulted in diminished treatment effect. Please see the full EOObesity technical report (submitted as an appendix) for further details. Updated obesity related comorbidity and life expectancy data from the EOOBesity model has been incorporated into a scenario analysis. The resulting cost-effectiveness results demonstrates the conservative nature of the company's and EAG's base-case approaches and demonstrates an addition QALY gain with setmelanotide when up to date comorbidity data are considered. 3. Clinical expert opinion Rhythm considers it important that the committee acknowledges the benefits demonstrated by setmelanotide and the ability of setmelanotide to improve patient quality of life. In particular, it should be recognised that clinical experts explained that whilst it might be possible for some patients to increase BMI/BMI-Z (whilst also experiencing improvement in hunger and hyperphagia), this would be very rare. Clinical experts also explained that this weight gain could be due to the impact of concomitant medications. Rhythm also notes that increase in weight could also be due to puberty and it should be considered that some children will undergo puberty earlier than average. Furthermore, benefits of reduced hyperphagia and an increase in hunger control should not be underestimated. Clinical experts noted during the appraisal committee meeting that patients who experience weight gain would still greatly benefit in terms of quality of life improvement due to a reduction in hyperphagia. A clinical expert statement notes *"improvement in hunger is important for quality of life in any person living with obesity. In the context of Bardet-Biedl syndrome control of hyperphagia in addition to hunger should be considered in its own merit and independently of weight loss."*.

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11	**Overview of the conservative nature of the model** Overall, Rhythm considers it highly important for the committee to recognise that the cost-effectiveness model for setmelanotide is conservative in several ways, as outlined below. **1. Treatment effect after discontinuation** The cost-effectiveness model does not account for tapering of treatment effect after setmelanotide discontinuation. Setmelanotide non-responders discontinuing treatment at the 14 weeks endpoint, were assumed to experience no treatment effect during Year 1 of the model. In addition, patients discontinuing after 52 weeks, were assumed to lose treatment effect at the time of discontinuation and return to their original BMI/BMI-Z score category. However, in clinical practice, these patients will still accrue benefits for several months. **2. Hyperphagia treatment effect** The model base-case assumes that all responders move to mild hyperphagia. The mechanism of action of setmelanotide and patient testimony suggests that some patients would also be moving to "no hyperphagia". However this has not been included within the modelling, despite the fact that it is anticipated that there will be patients that move to no hyperphagia rather than mild hyperphagia. **3. Hyperphagia at baseline** Aligned with the committee preference, Rhythm has updated the base-case to reflect a mix of hyperphagia severities at baseline to 75% severe hyperphagia and 25% moderate hyperphagia.. As discussed previously, because of the mechanism of action of setmelanotide, we expect the response rate (change in hyperphagia leading to change in eating habits leading to significant weight reduction) to be higher in patients with severe hyperphagia compared with patients with moderate hyperphagia. In clinical practice, this would lead to a further enrichment of patients with severe hyperphagia at baseline continuing therapy long term beyond the initial 14 weeks period. This additional enrichment is not reflected in the base-case. **4. Upper limit of BMI-Z class (>4)** The upper limit of BMI-Z classes included within the modelling was BMI-Z >4. This was to align with the ranges for which comorbidity data and impact on mortality data was available. However, it should be noted that this would be an underestimation of the risks in patients with a an extremely high BMI (note, in the RM-493-023 trials there were patients with BMI-Z of 5.5 or 7). **5. Rate of obesity-related comorbidities in early-onset obesity** As mentioned earlier, the EOObesity-model data (included as an addendum to this response), demonstrates that life expectancy for untreated patients is lower than initially expected. Incorporating the updated comorbidity data into a scenario analysis, demonstrates the conservative nature of the base-case and shows the setmelanotide is associated with more life year gains than in the base-case. **6. Limited list of co-morbidities associated with early-onset obesity** Early onset obesity is associated with a wide range of co-morbidities, impacting various aspects of a patients' quality of life. However, only a limited number of these are included

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	within the model. This includes recent findings on early-onset obesity being associated with a high prevalence of skin lesions, which have a detrimental effect on quality of life (Hasse et al., 2023). This is just one example of a co-morbidity not included within the modelling of setmelanotide cost-effectiveness. **7. Ethnic minority considerations** It should be considered that: • NICE guidelines on obesity (CG189) highlights that people from Black, Asian and minority ethnic family backgrounds "have an increased cardiometabolic health risk at lower BMI thresholds". • As a recessive disorder, BBS disproportionately affects people from ethnic background where consanguineous marriage is more commonly practiced. However, comorbidity data included within the model is mostly driven by data from Caucasian patients. This is likely to reflect an underestimation of co-morbidities and their impact in the overall target population.
12	**Overall summary of updates to the model to reflect committee preferences** • Assuming a mixed baseline distribution of severe and moderate hyperphagia • Inclusion of the BBSmultiplier calculated by the EAG with corrected mapping from the PedsQL scores in RM-493-023 • Inclusion of ongoing management of setmelanotide in local secondary care weight management clinics In addition, Rhythm has: • Provided rationale for maintaining other base-case preferences • Provided clarity on the approach to carer disutility • Used an alternative way to model treatment effect on BMI-Z (weighted average) • Provided clarity on the models ability to allow a variable treatment effect on hyperphagia, as well as a mixture of hyperphagia severities at baseline • Explored the potential regression to the mean for BMI-Z.
13	**Reference list** 1. Hasse, L et al. (2023). Pediatric obesity and skin disease: cutaneous findings and associated quality-of-life impairments in 103 children and adolescents with obesity." Endocrine connections vol. 12,9 e230235.

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	2. Haqq, A. et al. (2023). Impact of Setmelanotide on Future Metabolic Syndrome Risk in Pediatric Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation" at the Annual Meeting of the European Society for Paediatric Endocrinology, The Hague, The Netherlands, September 21-23, 2023 3. Haqq, A. et al. (2023). Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With Bardet-Biedl Syndrome. Accepted for "oral presentation" at The Obesity Society conference, 2023. 4. NICE (2023). Clinical guideline [CG189]. Obesity: identification, assessment and management 5. Pomeroy J et al. Bardet-Biedl syndrome: Weight patterns and genetics in a rare obesity syndrome. Pediatr Obes 2021;16:e12703

Insert extra rows as needed

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Appendix A: differences in moderate and severe hyperphagia as defined in the vignette study

	Moderate hyperphagia	Severe hyperphagia
Subjective experience	• You **usually do not feel full** after a **normally sized meal** • You become **hungry again within 1 hour** after eating a meal • Thinking about food **often interferes** with your **normal activities** of daily living	• You **almost never feel full** after a **normally sized meal** • You become **hungry again almost immediately** after eating a meal • Thinking about food **almost always interferes** with your **normal activities** of daily living
Observable behaviors	• You **often** overeat to the point of **discomfort** • You eat **more than 3 meals** per day with **more than 3 snacks** • You **often** eat during the **hour** before you go to bed • You **eat** a large number of calories when you wake up **during the night about 2-3 times per week** • You try to **sneak food** without people knowing about **twice per week**	• You overeat to the point of **discomfort at most meals** • You eat **almost constantly** • You eat during the **hour** before you go to bed **almost every night** • You **eat** a large number of calories when you wake up **during the night almost every night** • You try to **sneak food** without people knowing **almost every day**
Impact	• You become **moderately distressed or upset** when **denied food** • Because of hunger and eating behavior, you have **moderate problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behavior, you have **moderate problems with your relationships** with family and friends	• You become **extremely distressed or upset** when **denied food** • Because of hunger and eating behavior, you have **severe problems performing daily activities** such as self-care, getting around, leisure activities, and work or school • Because of hunger and eating behavior, you have **severe problems with your relationships** with family and friends
Weight	• You are at your **current weight**	• You are at your **current weight**

Early Onset of Obesity Model Technical-Report

21.08.2023

Executive Summary

The obesity epidemic is a global issue characterized by excessive body fat and associated with various chronic diseases. Driven by unhealthy eating habits and sedentary lifestyles, obesity has doubled since 1980, affecting over one billion people worldwide.

This report focuses on early-onset obesity, which is associated with greater long-term weight gain and higher risk of remaining obese. Due to diverse individual and health factors, quantifying the impact of early-onset obesity on morbidity and mortality is complex. To address this challenge, the Early-Onset of Obesity-Model (EOObesity-Model) was developed, integrating data from clinical studies and demographic information. This model provides insights into the effects of early-onset obesity and its relation to long-term morbidity and mortality, particularly cardiovascular health. Factors such as obesity level, age, and obesity duration influence the risk of comorbidities and mortality, with recent studies suggesting that reducing obesity duration can lower the long-term risk and severity of comorbidities[1].

This research assesses the consequences of obesity based on age, weight, and obesity duration. Data was extracted from studies that sufficiently quantified outcomes for incorporation into the EOObesity-Model. The study information was classified into three groups: Prevalence Information, Mortality Risk Information, and Duration Information.

Data on prevalence and mortality risk of various comorbidities such as Type 2 Diabetes, Cardiovascular Events, Non-Alcoholic Fatty Liver Disease, Cancer, Asthma, and Sleep Apnea were gathered for ages 0-100 years and BMI-Z 0.0-4.5. Impact of obesity duration information was collected for its effects on comorbidities and mortality risk. Prevalence and mortality risk information for all ages and weight classifications were tabulated, with missing information interpolated from existing data. Obesity duration tables were developed, containing risk increase Hazard Ratios for each year of obesity duration and obesity level. Irreversible risk accumulation due to obesity duration was also modeled based on studies assessing the effects of weight loss on comorbidity risk.

Comorbidity risk for each age is derived from by modifying prevalence with comorbidity-specific duration factors, further adjusted for irreversible risk accumulation to obtain a new risk profile following treatment for obesity (BMI reduction). This approach enables the estimation of comorbidity risks and life expectancy based on changing the weight trajectory, with comorbidity risks used to calculate disability-adjusted life years (DALYs).

The model creates two weight trajectories for each case: one without change in obesity severity/duration and one with a modified weight trajectory, allowing for assessment of the impact of this change on future comorbidity risks, life expectancy, and DALYs. These trajectories are “plotted” onto a three-dimensional risk landscape, influenced by individual patient factors such as comorbidity prevalence, mortality risk, obesity duration, and irreversible risk accumulation, and shift according to changes in obesity severity and duration, enabling precise estimations of obesity-related morbidity and mortality over the patient’s lifetime.

[1] Norris et al. 2020, Duration of obesity exposure between ages 10 and 40 years and its relationship with cardiometabolic disease risk factors: A cohort study
BMI-Z = body mass index z score

This model is unique in combining the currently best available evidence to allow for assessing the impact of early-onset obesity on mortality and morbidity, confirming the substantial impact of early-onset obesity on life expectancy and the benefits of early weight loss.

The model's capability lies in its systematic evaluation of a wide range of patient cases, validating findings for diverse scenarios. It reflects that increased weight and age, coupled with longer obesity duration, heighten the risk of comorbidities and mortality. The model's other ability is in assessing the risk reduction resulting from weight / BMI loss, linking greater and earlier weight / BMI loss to a larger reduction in comorbidity risk. This risk reduction decreases for each year of delay in change of weight trajectory, confirming the need for rapid diagnosis and intervention in early-onset obesity.

Table of Content

Initial Situation

The obesity epidemic is a global crisis that transcends borders, cultures, and socio-economic classes. Characterized by an excessive accumulation of body fat, obesity is not merely a cosmetic concern but a complex medical problem. It has more than doubled since 1980 and now affects over 650 million adults worldwide. At its core, the epidemic is driven by a modern lifestyle that often promotes unhealthy eating habits and sedentary behavior. The accessibility of high-calorie, low-nutrient food, and a shift away from physical labor have played significant roles in the rise of this public health challenge. The consequences of obesity are severe, leading to various chronic diseases like heart disease, diabetes, and certain cancers.

This work focuses primarily on a relatively under-researched form of early-onset obesity. With increasing level of obesity and early-onset, obesity related risks are increasing as well. Thus, an earlier onset of severe obesity also accelerates the development of comorbidities, leading to an earlier onset of severe consequences of obesity compared to patients with later onsets of obesity. An early-onset of obesity is also tending to lead to a higher level of obesity itself in patients compared to same age patients with a later onset of obesity. This early and greater long-term weight gain also leads to a higher risk of remaining obese compared to those with a later onset of obesity.[2] There is a paucity of work quantifying the impact of early-onset obesity on morbidity and mortality, especially on the long-term consequences, as the vast majority of work has been on general obesity and adult obesity, focusing on adulthood onsets and consequences in later adulthood.

Estimating the consequences of early-onset of obesity is a deeply intricate task that encompasses a broad spectrum of individual, health, economic, social, and methodological considerations. On the individual level, obesity's effects can vary widely due to different factors like genetics and lifestyle choices, making specific predictions difficult. Health-wise, obesity is linked to a diverse range of conditions, from heart disease and diabetes to certain types of cancer, complicating the task of estimating exact risks and interactions.

The economic impact, encompassing both direct costs like healthcare and indirect ones like productivity loss, requires nuanced understanding of various economic structures and societal values. The social and psychological facets of obesity, influenced by cultural norms and personal attitudes, add a layer of subjectivity that can be challenging to quantify. Further complexity arises from the necessity to differentiate between immediate and long-term consequences, as well as the complications introduced by co-morbidity with other health conditions. Lifestyle factors, such as diet and exercise, and the effectiveness of various interventions, can further muddy the waters in isolating obesity's consequences.

Finally, inconsistencies in defining and measuring obesity, such as the limitations of Body Mass Index (BMI), can lead to misclassification and challenges in assessing associated risks. In sum, the multi-dimensional nature of obesity, interwoven with various biological, psychological, economic, and societal factors, makes the task of estimating its consequences a complex and nuanced endeavor.

[2] Geserick et al. 2018, Acceleration of BMI in Early Childhood and Risk of Sustained Obesity

This technical report describes the innovative process by which we built a comprehensive model to estimate the effect of early onset of obesity on comorbidities and mortality risk. The Early-Onset of Obesity-Model (EOObesity-Model) adopts a multidisciplinary approach, synthesizing data from clinical studies and demographic information. The model is designed to navigate the inherent complexities and individual variations tied to obesity.

The subsequent sections detail the methodology, data sources, model architecture, validation processes, and key findings. This model was designed to serve not only as a sophisticated tool for healthcare professionals but also to inform Health Economic Modelling, as well as a foundation for future research in obesity's multifaceted consequences. Recent studies suggest that the long-term risk and severity of comorbidities linked to early onset obesity is lowered by reducing the duration of obesity[108]. Therefore, the main goal was to develop a disease estimation model to qualify and quantify the impact of early-onset obesity and its reduction on long-term morbidity and mortality with a specific focus on cardiovascular health & related diseases. In order to assess the consequences of early onset obesity in the light of all these factors and based on current research, the first step was to identify obesity related factors that have been best studied and shown to influence mortality and comorbidity.

- The first and most obvious factor is the level of obesity[25], which is measured by various methods in studies. Most common type of measurement is the BMI value, as well as the BMI Z-score in children and adolescents and the resulting percentile. Waist circumference and abdominal obesity have also been added recently. Although waist circumference and abdominal obesity are sometimes more accurate in assessing long-term risks, the overwhelming majority of studies measure BMI. In order to be able to draw on a larger pool of study results, BMI measurement was also chosen for the EOObesity-Model. The severity of obesity is directly related to an increase in the risk of comorbidities and an increase in the risk of mortality, therefore measuring the level of obesity allows a measurement of resulting risk increase in comorbidity risk as well as mortality risk.

- The second important factor is age[1]. Age in combination with weight defines a patient's risk of developing a certain comorbidity as well as their overall mortality risk. Being obese in old age increases these factors by a lot more than being obese in young adulthood.

- The combination of weight level and age directly leads to the third important factor, obesity duration. Besides the degree of obesity, the duration of obesity is important as well in developing comorbidities and increasing the mortality risk[108]. Someone who has been obese for 20 years has a significantly higher risk profile than someone of the same age and weight who has been obese for only 10 years. In order to better understand the effect of duration of obesity, numerous studies have been published in recent years that have precisely investigated this influence of duration.

- Living with severe obesity for a long period of time also leads to another development, namely the accumulation of irreversible processes that harm the organism and increase comorbidity risk. Juonala et al. (2014)[42] showed that these accumulated risks are irreversible when reducing the weight to average weight again. Thus, reducing the duration of obesity also decreases the time of this accumulation of irreversible risks, leading directly to smaller long-term risk.

Methodical approach

Below is a pictorial representation of the methodical approach used to determine the influence of the aforementioned factors on life expectancy and comorbidity risk. We have chosen two different approaches for the model, one for life expectancy and a separate approach for comorbidity risk determination. The reason for this is that a sufficient number of studies have quantified the impact of obesity on mortality and thus provide an accurate picture of the situation to provide the model with accurate information. In order to keep this mortality assessment as precise as possible, the comorbidity risk is assessed separately. Figure 1 shows the approach to modelling the impact of all the previously mentioned factors on mortality and thus on life expectancy. Figure 2 shows the approach to modelling the impact of all the above factors on the risk of developing comorbidities across the lifespan.

Figure 1: Methodical approach to model the mortality effect of early onset obesity

The first step is to gather all relevant patient information. This information yields comorbidity prevalence figures and mortality risks, which are combined to get one patient individual All-Comorbidity related Mortality risk. By further modifying this Mortality Risk with obesity duration, a patient individual trajectory is created that determines the Average and Maximum Life-Expectancy.

Figure 2: Methodical approach to model the morbidity effect of early onset obesity

In the second approach the previously gathered information on prevalence is directly modified with the effect of obesity duration, yielding another patient trajectory only representing the comorbidity risk development of the patient's life course.

Sources and Data Extraction

To assess the consequences of obesity based on age, weight as well as duration of obesity, we only considered studies that have quantified the resulting outcomes sufficiently enough to incorporate them into a model. In total, results of 226 Studies were assessed and 50 of those were included in the EOObesity-Model. assessing the prevalence of comorbidities in relation to BMI (BMI-Z Score) and age, as well as studies assessing the duration of obesity in relation to the severity of obesity were selected to extract data.

The data obtained in this way, is the cornerstone of all estimates, as the estimation process itself only combines these data sets to produce a case-specific estimate of mortality and morbidity. The study information was classified in three groups: Prevalence Information, Mortality Risk Information and Duration Information.

For reasons of comparability, the model works with BMI-Z Score for all age groups. Most studies report the weight of study participants over 18 years of age in BMI and that of those under 18 years of age in BMI-Z Score. In order to have a uniform weight unit for the entire life span, the BMI relevant study results were converted into BMI-Z score equivalents. As an intermediate step in this conversion, the BMI percentiles were added in order to obtain a uniform comparative value and to be able to assign BMI over 18 to the respective BMI-Z Scores. The weight range studied is between BMI 20 and BMI 50, which corresponds to a BMI-Z score range of 0.0 - 4.5, therefore covering also extreme levels of obesity. The reason for this upper limit is that most studies investigating obesity have investigated BMI 30 to 40 and very few studies have investigated and quantified higher levels of obesity. Due to a lack of reliable study results, it was decided to determine the obesity impact up to a BMI of 50. Conversely, this means that patients with a BMI above 50 have at least the same comorbidity risk as BMI 50 patients.

For the comorbidity prevalence information, data for Type 2 Diabetes (T2DM), Cardiovascular Events (CV) (Fatal non-fatal Events, Cardiovascular disease, coronary heart disease), Non-Alcoholic fatty Liver Disease (NAFLD) (NAFLD+ Non-Alcoholic Steatohepatitis), Cancer (all-cancer), Asthma, and Sleep Apnea were gathered for ages 0-100 years and BMI-Z 0.0-4.5.

For the Mortality Risk Information, data for Type 2 Diabetes, Cardiovascular Events (Fatal non-fatal Events, Cardiovascular disease, coronary heart disease), Non-Alcoholic fatty Liver Disease (NAFLD+NASH), Cancer (all-cancer), Asthma, and Sleep Apnea was gathered for ages 0-100 years and BMI-Z 0.0-4.5. The selection of these obesity related long-term outcomes has been driven by available literature and selected interviews with obesity experts.

Impact of obesity duration information was gathered for impact of duration on comorbidities and impact of duration on mortality risk. For the impact of duration on comorbidities, only studies for T2DM, CV, and cancer were available. Information for obesity duration between 0-20 years was available and one study provided risk increase data for each additional two years of obesity. Prevalence Information was needed for all ages 0-100 and all BMI-Z 0.0-4.5. Data extracted from the studies (Prevalence in %, Incidence in %, Hazard Ratios for BMI Classifications) was put into a table and missing information was interpolated only between given study results.

This resulted in a table giving comorbidity prevalence information for all ages and weight classifications required for modelling. For filling out the missing information in this table only interpolation was used and no extrapolation, to ensure the credibility of the results. The same approach was used to build the mortality risk tables for all comorbidities.

For obesity duration only information for the years of being obese and the level of obesity was needed. The tables were therefore filled with a risk increase Hazard Ratio for each year of obesity duration combined with the level of obesity in that year. In addition to pure risk increase due to duration of obesity, an irreversible risk accumulation was modelled as well. Information was available for T2DM and CV from studies assessing the effect of weight loss on comorbidity risk.

In the following section, each information extracted from study results is listed with a rationale for why which study was selected for data extraction.

T2DM Prevalence:

For the risk numbers at normal weight the DIABETES Surveillance of the Robert Koch Institute was used for ages 35 between 54. Tanamas et al. (2018)[1] was used to get information on younger ages and high BMI values. This Study was chosen as it provides prevalence and incidence numbers (5-year and 10-year incidence) for verry young and obese individuals, as well as a long follow up period until 45 years of age. Ahmad et al. (2014)[2] was chosen as it depicts the prevalence in young adulthood for both sexes and obese individuals. Bjerregaard et al. (2018)[3] was chosen as it has a big number of participants (n = 62,565), therefore depicting age and BMI specific prevalence numbers most accurately. It also includes a verry long follow up period until 30-60 years of age. (For the resulting risk plane, see Graphic 1 in Appendix)

Table 1: T2DM Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	Prevalence (%)	"	"	"	"	"	"
Hu 2014[1]	US	NHS	30-55 years	24 years follow up	Only Women	61,821	Can be used to "calibrate" for lower BMI values				3%	8%	-
Hu 2014[1]	US	NHS II	25-42 years	20 years follow up	Only Women	63,653	-	-	-	-	1%	3%	-
Ahmad 2014[2]	UK	HSE 2006	≥18 years	-	Both	9,425	-	-	17%	9%	3%	-	-
Tirosh 2011[3]	IL	MELANY	≥25 years	mean follow-up, 17.4 years	Only Men	37,674	-	-	-	-	-	7%	-
Luo 2019[4]	AU	ALSWH	18-23 years	19 years follow up	Only Women	11,192	Studies selected	-	-	-	7%	3%	3%
Abdullah 2010[5]	US	FHS	28–62 years	48 years follow up	Both	1,256	-	-	-	-	22%	-	-
Tanamas 2018[6]	US	American Indians	5-18	until 45 years Age	Both	7,045	-	17%	15%	6%	3%	-	-
Bjerregaard 2018[7]	DK	CSHRR	7-13 years	until 30-60 years Age	Only Men	62,565	-	-	-	-	31%	18%	14%

1) Hu et al. Duration of Obesity and Overweight and Risk of Type 2 Diabetes Among US Women, 2014 2) Ahmad et al. Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey, 2014 3)Tirosh et al. Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis, 2011 4) Luo et al. Age of obesity onset, cumulative obesity exposure over early adulthood and risk of type 2 diabetes, 2019 5) Abdullah et al. The duration of obesity and the risk of type 2 diabetes, 2010 6) Tanamas et al. Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population, 2018 7) Bjerregaard et al. Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes, 2018

Cardiovascular Event Prevalence:

First study included is Ahmad et al. (2014)[2], due to its information on highly obese individuals of both sexes. Second study, containing most information is Baker et al. (2007)[10]. This study included 276,835 individuals from the Danish CRS databank. Individuals from 7 to 60 years are included and all obesity classifications are included for both sexes. (For the resulting risk plane, see Graphic 2 in Appendix)

Table 2: CV Event Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Prevalence (%)	"	"	"	"	"	"
Ahmad 2014[1]	UK	HSE 2006	≥18 years	-	Both	9,425	-	-	11%	8%	4%	-	-
Baker 2007[2]	DK	Danish CRS	7-13 years 25-60 years	46 years of follow up	Both	276,835	(increase in Relative Risk = 1.17 (CI 1.15-1.20) or 1.9%per 5.6 Kg weight increase) 40%	36%	32%	26%	23%	19%	15%
Kim 2021[3]	12 systematic reviews, 53 meta-analyses (501 non-overlapping cohort studies) and 12 MR studies (25 cohorts)		Meta-Analysis				(increase in risk of cardiovascular event per BMI 5 Units = 1.4) 41%	37%	29,4%	26,6%	21%	-	-
Sierra-Johnson 2005[4]	DE	-	62 ±11 years	6.4 ±1.8 years	Both	389	-	-	-	-	26%	29%	16%
Liu 2019[5]	CN	-	51.5 ± 11.1 years	2006-2015	Both	18,703	-	-	-	-	-	HR 1.3	HR 1
Li 2006[6]	SE	MDC	48-67	7.6±1.7 years	Both	27,007	-	-	-	HR 2.04/2.14	HR 1.67/1.69	HR 1.2/1.4	HR1
Khan 2018[7]	US	10 Cohorts	20-79	1964-2015	Men/Women	190,672	-	-	65%/47%	47%/38%	47%/38%	37%/28%	32%/20%

1) Ahmad et al. Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey, 2014 2) Baker et al. Childhood Body-Mass Index and the Risk of Coronary Heart Disease in Adulthood, 2007 3) Kim et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies, 2021 4) Sierra-Johnson et al. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation, 2005 5) Liu et al. Joint association of body mass index and central obesity with cardiovascular events and all-cause mortality in prediabetic population: A prospective cohort study, 2019 6) Li et al. Sex differences in the relationships between BMI, WHR and incidence of cardiovascular disease: a population-based cohort study, 2006 7) Khan et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity, 2018

NAFLD Prevalence:

For childhood ages Anderson et al. (2015)[15] was used as it included children from 1 to 19 years of age and nearly all obesity classifications. Schwimmer et al. (2006)[51] and Arshad et al. (2021)[17] were taken to model the prevalence at young adulthood as they included participants between 2 and 29 years of age. Data from Younossi et al. (2016)[18] provided information for all ages between 30 and 79 years of age, but no information on BMI differences. To model the BMI differences as well, Information from Mummadi et al. (2008)[16] was included as it depicted the prevalence of NAFLD in highly obese adult individuals. (For the resulting risk plane, see Graphic 3 in Appendix)

Table 3: NAFLD Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Prevalence (%)	"	"	"	"	"	"
Anderson 2015[1]	corresponding to 76 independent study populations		1-19 years	Systematic Review/Meta Analysis of 74 Studies			-	-	49%	36%	25%	17%	9%
Schwimmer 2006[2]	US	SCALE	2-19 years	1993-2003	Both	742	-	-	-	-	38%	20%	17%
Arshad 2021[3]	US	NHANES	12-29 years	2007-2016	Both	4,654	-	-	-	-	-	-	12%/25%/ 22%
Younossi 2016[4]	meta-analysis		30-79 years of Age		Both	8,515,431	Only Age specific Data available 30-79 years 30-39=22%; 40-49=26%; 50-59=27%; 60-69=29%; 70-79=34%						
Mummadi 2008[5]	electronic literature search of published articles on bariatric surgery and liver histology (total of 15 studies (766 paired liver biopsies))						-	95%	85%	70%	-	-	-
Le 2017[6]	US	NHANES	18+ years	1999-2012	Both	6000	-	-	90%	80%	-	30%	20%
Stefan 2018[7]	Citing Anderson 2015 and Younossi 2014												
Vernon 2011[8]	Systematic review 1980-2010						-	-	-	-	98%	57%	25%

1) Anderson et al. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis, 2015 2) Schwimmer et al. Prevalence of Fatty Liver in Children and Adolescents, 2006 3) Arshad et al. Nonalcoholic Fatty Liver Disease Prevalence Trends Among Adolescents and Young Adults in the United States, 2007-2016, 2021 4) Younossi et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes, 2016 5) Mummadi et al. Effect of Bariatric Surgery on Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis, 2008 6) Le et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States, 2017 7) Stefan et al. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies, 2018 8) Vernon et al. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults, 2011

Cancer Prevalence:

For childhood prevalence number, information from Ward et al. (2014)[24] was extracted and used to model the cancer prevalence for children and adolescents. This study provided a big part of the US population (SEER+NAACCR Cohorts) from birth onwards. For adulthood Yao et al. (2022)[25] was used as the study provides prevalence information for all ages between 20 and 90 years with a total cohort of n = 503,060. To model the differences caused by BMI classifications, Hazard Ratios were extracted from Jee et al. (2008)[26]. This study included 1,213,829 patients and therefore precisely depicts the impact of weight on cancer risk. (For the resulting risk plane, see Graphic 4 in Appendix)

Table 4: Cancer Prevalence Study Selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Prevalence (%) or HR	„	„	„	„	„	„
Ward 2014[1]	US	SEER	Birth	1975 and 2010	Both	28% of US population	-	-	-	-	-	-	0,35%/0,25%
Ward 2014[1]	US	NAACCR	Birth	1975 and 2010	Both	95% of US population	-	-	-	-	-	-	**0,35%/0,25%**
Yao 2022[2]	CA	CCR	all	2013-2018	Both	503,060 cases the past 5-years	Only Age specific Data available 20-90 years 20-29= 0,3% 30-39= 0.83%; 40-49=1,89%; 50-59=4,22%; 60-69=8,44%; 70-79=13,6% 80-89=14,63% 90+=11,13%						
Jee 2008[3]	KR	NHIC	30-95 years	1992-1995	Both	1,213,829	-	-	HR 1.49	HR 1.33	HR 1.19	HR 1.03	HR 1
RKI 2021[4]	DE	-	-	2017-2018	Men/Women	90%+ of Germany	Only Age specific Data available 45-85 years 45= 2.2%/1.2% 55 = 4.8%/3.3% 65 = 8.2%/9.7% 75 = 12.8%/20% 85 = 16.2%/26.7%						
Wang 2020[5]	CN	CKB	51.47±10.67	median: 8.95 years	Both	508,362	-	-	-	-	HR 1.13	HR 1	HR 1
Wang 2020[5]	CN	CKB	51.47±10.67	median: 8.95 years	Both	508,362	-	-	-	-	-	4,2%	4.2%

1) Ward et al. Childhood and Adolescent Cancer Statistics, 2014, 2014 2) Yao et al. Short-term cancer prevalence in Canada, 2018, 2022 3) Jee et al. Body mass index and cancer risk in Korean men and women, 2008 4) Robert Koch-Institut, Krebs in Deutschland für 2017/2018, Zentrum für Krebsregisterdaten, 13. Ausgabe, Berlin, 2021 5) Wang et al. Cancer incidence in relation to body fatness among 0.5 million men and women: Findings from the China Kadoorie Biobank, 2020

Asthma Prevalence:

Information from the CDC Most recent national Asthma data 2020[30] was used to model the Asthma prevalence at normal weight from ages 0-65 years of age. For later ages Chen et al. (1999)[31] was used, as it provides information until 70 years of age. To model the differences caused by BMI classifications, Hazard Ratios from Kim et al. (2003)[32] were used. This study assessed the impact of BMI on the development of asthma in 45,973 individuals until a BMI of 45. (For the resulting risk plane, see Graphic 5 in Appendix)

Table 5: Asthma Prevalence Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Prevalence (%) or HR	„	„	„	„	„	„
Kim 2003[1]	US	2000 BRFSS	18-34 years	-	Both	45,973	-	HR 4.9	HR 3.19	HR 2.28	HR 1.79	HR 1.51	HR 1
Camargo 1999[2]	US	NHS II	24-44 years	191-1995	Women	116,678	-	-	HR 3.1	HR 2.6	HR 2.3	HR 1.5	**HR 1**
Nystad 2004[3]	NO	Screening Programm	14–60 years	1963–2002	Both	135,405	-	-	-	HR 2.34	HR 1.78	HR 1.27	**HR 1**
KIM 2003[1]	US	2000 BRFSS	18-34 years	-	Both	45,973	-	-	-	-	-	-	8%
Chen 1999[4]	CA	NPHS	≥12 years	1994-1995	Women	17,605	(Age specific Prevalence 12-70+ years) 12-24 years = 10.4%; 25-39 = 5.8%; 40-54 = 4.1%; 55-69 = 4.9%; 70+ = 4.5 %						
Zhang 2022[5]	204 countries	GBD	1-19 years	1990-2019	Both	-	(Age specific Prevalence 1-19 years) 1-4 years= 44.2%; 5-9 years = 28.4%; 10-14 years= 16.7% 15-19 years= 10.8%						
CDC[6] Most Recent National Asthma Data Prevalence 2020							(Age specific Prevalence 0-65+ years) 0-4=2%; 5-11=5.9%; 12-14= 8.1%; 15-19=9.3%; 20-24=10.3%; 25-34=8.1%; 35-64=8.3%; 65+=7.8%						
Huisstede 2013[7]	NL	pre-operative screening before bariatric surgery	18-60 years	2009-2011	Both	86	-	42%	-	-	-	-	-

1) Kim et al. Sex-race Differences in the Relationship between Obesity and Asthma: The Behavioral Risk Factor Surveillance System, 2000, 2003 2) Camargo et al. Sex-race Differences in the Relationship between Obesity and Asthma: The Behavioral Risk Factor Surveillance System, 2000, 2003, 1999 3) Nystad et al. Body Mass Index in Relation to Adult Asthma among 135,000 Norwegian Men and Women, 2004 4) Chen et al. Increased Effects of Smoking and Obesity on Asthma among Female Canadians: The National Population Health Survey, 1994-1995, 1999 5) Zhang et al. The Burden of Childhood Asthma by Age Group, 1990–2019: A Systematic Analysis of Global Burden of Disease 2019 Data, 2022 6) Centers for Disease Control. Most recent national asthma data 2020 7) Huisstede et al. Underdiagnosis and overdiagnosis of asthma in the morbidly obese, 2013

Sleep Apnea Prevalence:

Verlhust et al. (2007)[36] provides an overview of obese children affected by Sleep Apnea. For modelling Adulthood ages Lopez et al. (2008)[37] and Young et al. (2002)[35] were used. Lopez provides data on all BMI classifications needed for modelling and Young provides all information needed for all ages after childhood. (For the resulting risk plane, see Graphic 6 in Appendix)

Table 6: Sleep Apnea Prevalence Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Prevalence (%) or HR	„	„	„	„	„	„
Verlhust 2007[3]	BE	Pediatric Clinic	6-16 years	2002-2005	both	91	-	-	-	-	47%	44%	-
Lopez 2008[2]	US	Clinic Database	17-75 years	5 years	both	290	77%	73%	73%	71%	33%	33%	-
Young 2002[1]	US	SHHS	40-98 years	questionnaire	both	5615	(Age specific prevalence 40-85 years) 39-49=10%; 50-59=16%; 60-69=19%; 70-79=21%; 80-99=20%						
Young 2002[1]	US	SHHS	40-98 years	questionnaire	both	5615	(Severetiy differences in OSA) Mild OSA=3-28%; Severe OSA=1-14%						

1) Young et al. Epidemiology of Obstructive Sleep Apnea A Population Health Perspective, 2002 2) Lopez et al. Prevalence of Sleep Apnea in Morbidly Obese Patients Who Presented for Weight Loss Surgery Evaluation: More Evidence for Routine Screening for Obstructive Sleep Apnea before Weight Loss Surgery, 2008 3) Verhulst et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution, 2007

T2DM Mortality Risk:

Carstensen et al. (2020)[4] and Salehidoost et al. (2018)[5] provides a broad spectrum of patient information regarding age and mortality risk due to diabetes. It assessed the mortality risk of 448,445 diabetic patients in Denmark and was chosen to model the age differences in mortality risk. To Modell the BMI differences Mulnier et al. (2005)[6] was used. This study provides data for all BMI Classifications and a broad diabetic cohort (n = 44,230) and a reference group without diabetes (n = 219,797). The mortality risk was adjusted by 58% for (Cardiovascular mortality 44% + Cancer 14%) based on Liu et al. (2019)[7], to tackle double counting in the modelling. (For the resulting risk plane, see Graphic 7 in Appendix)

Table 7: T2DM Mortality Risk Study selection

Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
							Mortality (%) or HR	„	„	„	„	„	„
Carstensen 2020[1]	DK	entire Danish population	0-100 years	1996-2016	both	448,445 diabetics	Only Age specific Data available 0-80+ Age 10-45 = 0,05%-0,5%; 50-80 = 0,7%-7%; 85-100 = 10%-75%						
Salehidoost 2018[2]	IR	database of the Isfahan Endocrine and Metabolism Research Center	Mean Age 49.4-56.0	1992-2010	both	2,383	-	-	HR 1.17	HR 0.68	HR 0.8	HR 0.82	HR 1
Mulnier 2005[3]	UK	GPRD	35 – 89 years	1992-1999	both	44,230 diabetics + 219,797 reference	HR 1.59	HR 1.43	HR 1.28	HR 1.22	HR 1.13	HR 0.97	HR 1
Shan 2020[4]	CN	From: Tianjin, Shenyang, Taiyuan, Rizhao.	Mean Age 44.12 years	12-years observation	both	39,054	-	-	-	-	-	-	0,14%
Lin 2012[5]	TW	DCMP	30-94 years	Median 4.02 years	both	5,686	-	-	-	-	-	-	0.5%

1) Carstensen et al. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016, 2020 2) Salehidoost et al. Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus, 2018 3) Mulnier et al. Mortality in people with Type 2 diabetes in the UK, 2005Source: Exemplary literature screen for relationship of Early Onset Obesity and Prevalence of T2DM 4) Shan et al. Associations between the incidence and mortality rates of type 2 diabetes mellitus and long-term exposure to ambient air pollution: A 12-year cohort study in northern China, 2020 5) Lin et al. Impact of Lifestyle-Related Factors on All-Cause and Cause-Specific Mortality in Patients With Type 2 Diabetes, 2012

Cardiovascular Event Mortality Risk:

Data for all ages (0-70+) was provided by the Global burden of disease study 2019[11,12]. Information from Furer et al. (2018)[13] was taken to model the differences in mortality risk caused by increased BMI level. Furer included 2,294,139 patients to assess the impact of BMI on cardiovascular mortality risk between 1967 until 2010. (For the resulting risk plane, see Graphic 8 in Appendix)

Table 8: Cardiovascular Event Mortality Risk Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	Mortality (%) or HR	„	„	„	„	„	„
GBD 2019[1]	all	-	-	1990-2019	both	Global	Only Age specific Data available 0-70+ 5-14 years = 0.001%; 15-49 years = 0.04%; 50-69 years = 0.5%; 70+ years = 3.56%						
Furer 2018[2]	IL	All Military examination	17 years	1967-2010	both	2,294,139	-	-	HR 7.5/6.7	HR 4.2/5.7	HR 2.4/4.8	HR 2.3/3.1	HR 1/1
Gunnel 1998[3]	US	Boyd Orr	2-14 years	1948-1995	both	2,399	-	-	-	-	-	HR 2.6	-
Gunnel 1998[3]	US	Boyd Orr	2-14 years	1948-1995	both	2,399	-	-	-	-	-	-	0,3%
Lin 2012[4]	TW	DCMP	30-94 years	median 4.02 years	both	5,686	-	-	-	-	-	-	0.4%
Sierra-Johnson 2005[5]	DE	-	62 ±11 years	6.4 ±1.8 years	both	389	-	-	-	-	2%	8%	10%
Khan 2018[6]	US	10 Cohorts	20-39	1964-2015	Male/Female	190,672	-	-	3.8%/0%	1.7%/1%	1.7%/1%	0.9%/0.4%	0.6%/0.4%
Khan 2018[6]	US	10 Cohorts	40-59	1964-2015	Male/Female	190,672	-	-	35%/19.5%	24%/18.3%	24%/18.3%	18.2%/12%	16.2%/8.9%

1) Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME) 2) Furer et al. Sex-specific associations between adolescent categories of BMI with cardiovascular and non-cardiovascular mortality in midlife, 2018 3) Gunnel et al. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort, 1998 4) Lin et al. Impact of Lifestyle-Related Factors on All-Cause and Cause-Specific Mortality in Patients With Type 2 Diabetes, 2012 5) Sierra-Johnson et al. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation, 2005 6) Khan et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity, 2018

NAFLD Mortality Risk:

Le et al. (2017)[22] and Simon et al. (2021)[21] were used to model age differences in mortality risk due to NAFLD, as all ages are covered by these two studies. To model the additional differences caused by BMI, information from Golabi et al. (2020)[23] is taken as it provides data for patients aged 20-74 years and uses data from NHANES III. (For the resulting risk plane, see Graphic 9 in Appendix)

Table 9: NAFLD Mortality Risk Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	Mortality (%) or HR	„	„	„	„	„	„
Le 2017[1]	US	NHANES	18+ years	1999-2012	both	6000	-	-	-	-	-	-	0,5%
Simon 2021[2]	SE	ESPRESSO	≤25 years	1966–2017	both	718	-	-	-	-	-	-	0,39%
Golabi 2020[3]	US	NHANES III	20-74 years	18.7-22.4 years follow up	both	9,341	-	-	-	HR 2.48	HR 1.84	HR 2.54	HR 1
Younossi 2014[4]	meta-analysis		30-79 years of Age		both	8,515,431	-	-	-	-	-	1%	-
Rafiq 2009[5]	US	CCF+CLD	50.2 ±14.5 years	28.5 years	both	173	-	-	-	-	2.7%	-	-

1) Le et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States, 2017 2) Simon et al. Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality, 2021 3) Golabi et al. Mortality of NAFLD According to the Body Composition and Presence of Metabolic Abnormalities, 2020 4) Younossi et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes, 2016 5) Rafiq et al. Long-Term Follow-Up of Patients With Nonalcoholic Fatty Liver, 2009

Cancer Mortality Risk:

Miller et al. (2020)[27] covers around 28% of US population with its study results and depicts the mortality risk for all ages needed for modelling. Calle et al. (2003)[28] was chosen for modelling the BMI differences because here too the cohort (n = 900,053) is exceptionally big, depicting a precises picture of BMI differences on cancer related mortality risk. (For the resulting risk plane, see Graphic 10 in Appendix)

Table 10: Cancer Mortality Risk Study Selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Mortality (%) or HR	„	„	„	„	„	„
Miller 2020[1]	US	SEER	15-39 years	1975-2016	both	28% of US population	Only Age specific Data available 15-40+ years 15-19 years = 3%; 20-29 years = 2.8% 30-39 years = 3.4%; 40+ = 6,8%						
Calle 2003[2]	US	Cancer Prevention Study II	30+ years	1982- 16 years of follow up	both	900,053		HR 2.05	HR 1.52	HR 1.2	HR 1.09	HR 0.97	HR 1
RKI 2021[3]	DE	-	-	2017-2018	Women/Men	90%+ of Germany	-	-	-	-	-	-	7.8%
Bhaskaran 2018[4]	UK	CPRD	16 years and older	1998-2016	both	1 969 648	-	-	HR 1.45	HR 1.24	HR 1.11	HR 1.06	HR 1
Bhaskaran 2018[4]	UK	CPRD	16 years and older	1998-2016	both	1 969 648	-	-	-	-	20%/12%/5.6%/2%	19.6%/11%/4.7%/1.8%	17.6%/9.8%/4.2%/1.7%

1) Miller et al. Cancer Statistics for Adolescents and Young Adults, 2020, 2020 2) Calle et al. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults, 2003 3) Robert Koch-Institut, Krebs in Deutschland für 2017/2018, Zentrum für Krebsregisterdaten, 13. Ausgabe, Berlin, 2021 4) Bhaskaran et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK, 2018

Asthma Mortality Risk:

Data on Asthma Mortality Risk for Age was gathered from the Supplementary material provided by Lemmetyinen et al. (2018)[34] and BMI specific data from Whitlock et al. (2009)[33]. The difference in mortality risk due to BMI was assessed based on a collaborative analysis of 57 prospective studies combining 894,576 patients. (For the resulting risk plane, see Graphic 11 in Appendix)

Table 11: Asthma Mortality Risk Study selection

							(BMI >50)	(BMI 45-50)	(BMI 40-45)	(BMI 35-40)	(BMI 30-35)	(BMI 25-30)	(BMI 20-25)
Study	**Country**	**Cohort**	**Age Baseline**	**Observation period**	**Men and/or Woman**	**N**	Prevalence (%) or HR	„	„	„	„	„	„
Jordan 2010[1]	US	NHANES III	17-80+ years	1988-1994	both	2439	-	-	HR 5.78	HR 1.69	HR 1	HR 1.25	HR 1.45
Zhang 2022[2]	204 countries	GBD	1-19 years	1990-2019	both	-	(Age specific Mortality all Population 1-19 years) 1-4 = 0,0012%; 5-9 = 0,0003%; 10-14 = 0,0003%; 15-19 = 0,0005%						
Lemmetyinen 2018[3]	FI	questionnaire in 1997	30 years	Mean 15.6 years	both	1052	-	-	-	-	-	-	0,012%
Whitlock 2009[4]	Collaborative analysis of 57 prospective studies				both	894,576	-	-	-	HR 1.39	HR 1.15	HR 0.94	HR 1
CDC[5] Most Recent National Asthma Data Mortality 2020							(Age specific Mortality all Population 0-65+ years 0-4=-; 5-11=0,00032%; 12-17=0.00039%; 25-43=0,00076%; 35-64=0,0013%; 65+= 0,003%						

1) Jordan et al. Obesity and Mortality in Persons with Obstructive Lung Disease Using Data from the NHANES III, 2010 2) Zhang et al. The Burden of Childhood Asthma by Age Group, 1990–2019: A Systematic Analysis of Global Burden of Disease 2019 Data, 2022 3) Lemmetyinen et al. Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort, 2018 4) Whitlock et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies, 2009 5) Centers for Disease Control. Most recent national asthma data 2020

Obesity Duration impact on Mortality Risk:

Abdullah et al. (2011)[38] provides a detailed analysis of the duration of obesity and the impact on all-cause mortality risk. It assesses under one year of duration until over 25 years of obesity duration and assessed obese individuals from 28 years until 62 years of age. (For the resulting risk plane, see Graphic 12 in Appendix)

Table 12: Obesity Duration impact on Mortality Risk Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Abdullah 2011[1]	US	FHS	28-62	48 years	Both	5036	1	1.51	1.94	2.25	2.52
Abdullah 2011[1]	US	FHS	28-62	48 years	Both	5036	1	1.06	1.16	1.29	1.25

1) Abdullah et al. The number of years lived with obesity and the risk of all-cause and cause-specific mortality, 2011

Obesity Duration impact on T2DM Risk:

Hu et al. (2015)[39] assessed the impact of duration of obesity on the development of T2DM in 125,474 individuals (NHS+NHSII). The study adjusted results for all BMI classifications leaving only the effect of duration for observation. Hazard Ratios from this study were used to increase T2DM risk correspondingly to duration of obesity. (For the resulting risk plane, see Graphic 13 in Appendix)

Table 13: Duration impact on T2DM Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Hu 2015[1]	US	NHS / NHSII	25-55	1984-2011	Women	125,474	1	1.58	1.43	1.11	1.11
Hu 2015[1]	US	NHS / NHSII	25-55	1984-2011	Women	125,474	1	1.04	1.14	1.26	1.34

1) Hu et al. Duration of obesity and overweight and risk of type 2 diabetes among US women, 2015

Obesity Duration impact on Cardiovascular Event Risk:

In 48 years of observation Abdullah et al. (2014)[40] made clear, that the duration of obesity has a significant impact of on the development of Cardiovascular Events in obese individuals. Hazard ratios were extracted and used to increase the risk accordingly to specific obesity durations. (For the resulting risk plane, see Graphic 14 in Appendix)

Table 14: Duration impact on Cardiovascular Event Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Abdullah 2014[1]	US	FHS	28-62	48 years	Both	5036	1	1.28	1.31	1.5	1.59

1) Arnold et al. Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States, 2016

Obesity Duration impact on Cancer Risk

Arnold et al. (2016)[41] assessed the development of all cancer types linked to obesity duration in 73,913 individuals from the WHI cohort between 1993-1998. Hazard Ratios were extracted as well and considered when modelling the effect obesity duration. (For the resulting risk plane, see Graphic 15 in Appendix)

Table 15: Duration impact on Cancer Study selection

							>1 year	1-4.9 years	5-14.9 years	15-24.9 years	≥25 years
Study	Country	Cohort	Age Baseline	Observation period	Men and/or Woman	N	HR	"	"	"	"
Arnold 2016[1]	US	WHI	50-79	1993-1998	Women	73,913	1	1	1.09	1.18	1.22

1) Arnold et al. Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States, 2016

Irreversible Risk Accumulation Integration:

Juonala et al. (2008)[42] assessed the impact of weight loss on the cardiometabolic risk profile of 6328 participants. For T2DM and CV Events the risk profile of patients that have lost weight was higher than that of patients that were never obese, indicating a risk accumulation that is nonreversible. To Get Hazard Ratios needed for modelling, we compared those cases to the known impact of obesity duration and conservatively took the difference as new hazard ratios to be able to model the impact of varying durations of obesity and the resulting irreversible accumulated risk in that period. These new Hazard Ratios describing the irreversible risk accumulation share of comorbidity risks over time were implemented into the modelling process of estimating the case specific comorbidity burden. Risk accumulation for NAFLD was based on one study assessing effect of bariatric surgery by Mummadi et al. (2008)[46] (Graphics 16,17,18).

Model Framework

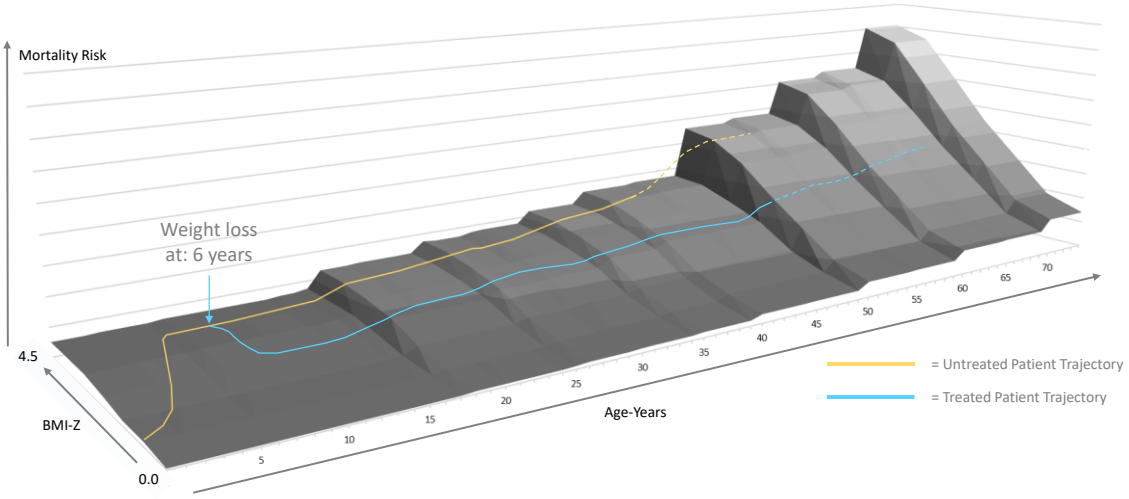
Methodology of modelling outcomes of obesity and weight development

The data tables described above allow access to all the information needed to generate all combinations of weight (BMI-Z 0.0-4.5), age (0-100 years) and duration of obesity (0-100 years). These combinations allow the generation of patient specific trajectories and to assess future comorbidity risks and the corresponding life expectancy.

The prevalence and mortality risk tables serve as the basis for these assessments. The combination results in a mortality risk that is further modified by mortality specific duration factors to obtain a life expectancy estimation. By modifying the prevalence only, with comorbidity specific duration factors the comorbidity risk for each specific age is yielded. This comorbidity risk is further adjusted for the irreversible risk accumulated, to obtain the new risk profile after treatment (after weight loss). These processes are always the same and are only influenced by the age and weight development entered into the model. With this approach, it is possible to estimate how the comorbidity risks and life expectancy will develop based on the patient's weight development. The comorbidity risks are needed to further calculate the disability adjusted life years (DALYs).

In order to be able to see an effect resulting from a weight reduction, the model creates two weight development pathways for the same base case. One pathway without weight reduction and one pathway with new weight development. The resulting difference in risk and life expectancy as well as DALYs after weight reduction is the impact that this reduction has on the future development of comorbidity risks and life expectancy. The created pathways are located in a three-dimensional risk landscape. This risk landscape is a direct result of the individual patient factors, namely prevalence, mortality risk as well as obesity duration and irreversible risk accumulation. The pathway shifts on this risk landscape created by the model engine according to its weight development. The following is an example of a Mortality-Risk-Landscape with two different trajectories representing stable weight at BMI-Z 4.0 in yellow and a weight loss scenario to BMI-Z 3.0 represented in blue (Figure 3).

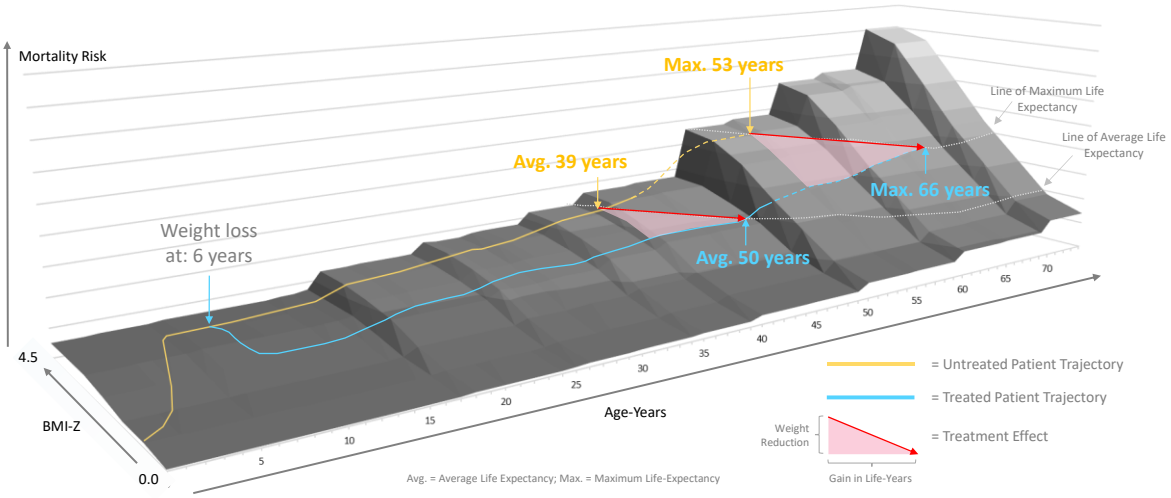
Figure 3: Patient corresponding Mortality-Risk-Landscape



Source: EOObesity-Model

The weight development trajectories are yielding risk information that are used to calculate the mortality risk and the comorbidity risk for all ages. As explained earlier, the difference in the results of the different pathways gives the effect of weight loss on mortality and comorbidity risks. Below is an example where the movement of trajectories on the mortality Risk-Landscape leads to different life expectancies (Figure 4).

Figure 4: Patient corresponding Mortality-Risk-Landscape with Life-Expectancy



Source: EOObesity-Model

Model Step-by-Step assembly

The Actual Model consist of three main bodies: The Interface to create a case specific weight development pathway, the engine that is selecting case specific information based on the provided weight development pathway and calculates comorbidity risks as well as a life expectancy, and the database, which provides all the information extracted by the engine.

First step of building the model was to create the database containing all information needed to model different case scenarios. For each combination of age between 0-100 years and a BMI-Z Score of 0.0-4.5 a comorbidity risk is given. Depending on the onset of obesity for each year of obesity duration and BMI-Z between 0.0-4.5 a specific duration risk increase is given. The Duration Factor Table was created using the Hazard Ratios provided by the afore mentioned studies. These Hazard Ratios were then taken as values for the average study BMI and the upper Confident Intervals were taken as values for the maximum BMI value. The remaining BMI values were interpolated between these data points and no risk increase for BMI-Z of 0.0.

To counter overestimating when modifying the comorbidity risk with duration factors, we adjusted those duration factors for the average obesity duration in the corresponding study cohorts. This step was made based on the assumption, that in a relatively older cohort obesity duration is longer than in a cohort with younger individuals, resulting in an overestimation for the younger and an underestimation for the older patients when taking the same risk value for both age groups. (Graphics 19,20,21,22)

For the comorbidities: T2DM, CV, NAFLD, Cancer, and Asthma Disability Weights are given, needed for DALY calculation. To implement the irreversible risk accumulation of some comorbidities data was created for each age between 0-100 years and all BMI-Z Score 0.0-4.5.

Second step was to create an engine capable of extracting data from the database and calculating Life-Expectancy as well as comorbidity risks for all ages. Another part is the DALYs calculation happening separately. Based on the Age and Weight at that point the engine is calculating the duration of obesity. With The Age, BMI-Z, and Obesity Duration the engine can fill out all the missing information provided by the database.

The third and final step was to build an interface for data entry and to build an interface between the interface and the engine that generates the weight development paths based on the data entered into the interface. This generated weight development pathway is directly flowing into the engine which provides all the necessary information for the engine to start modelling. The user does not have to leave the interface to see the results, as all information generated by the engine is visible on the interface. In parallel with the data entry, the life expectancy, the DALY overview, and the comorbidity risks for all ages are presented for the treated and untreated patient (No weight loss and weight loss).

This resulting model does not take ethnic and sex differences as well as “healthy-obese” into account.

Case Example

To be able to compare our findings we created a base case example patient with early onset of obesity. Patient conditions were a BMI-Z of 2.5 at 2 years of age and BMI-Z of 4.0 at 4 years of age. This information was used to generate a first patient pathway resembling an untreated patient. With the same weight development at the early stages of life, the patient lost weight at 6 years of Age resulting in a new weight of BMI-Z 3.0, leading to the second Pathway resembling the treated patient. The weight loss at 6 years of Age resulted in a gain in Life-Years of [redacted] years and a reduction of [redacted] DALYs. Later Age years at weight reduction let to diminished treatment effects. Down below is a graphical representation of Three different case Scenarios: Untreated patient, Treatment at 6 years and 20 years:

Figure 5: No Weight reduction

Figure 6: Weight reduction at 6 years of age

Figure 7: Weight reduction at 20 years of age

Model Conclusions

The quantification of the model and the systematic run-through of a wide variety of patient cases is one ability of the model and provides validation for a wide variety of findings. The most important dynamics of the model reflect the findings already discussed in the afore mentioned studies. Increased weight as well as higher age is associated with a higher risk of all comorbidities. This risk increases additionally with higher duration of obesity. An additional dynamic that was not integrated into the model for technical reasons is the increase in risk due to multimorbidity. Having one specific morbidity increases the risk of developing another additional comorbidity, for example the onset of T2DM increases further the risk of CV events. The integration of this additional factor affected all calculations and thus had a severe impact on life expectancy and the overall assessment of comorbidity risk. However, the model results no longer correspond to the clinically verifiable reality, after implementation. Reason for this is double counting a certain number of comorbidities. If you add all prevalence numbers in the model for a certain age and specific weight, sometimes the total comorbidity prevalence exceeds 100%, for example at 15 years of age and a BMI-Z of 3.0 all comorbidities combined yield a prevalence of 120%. This means that at least 100% of all people have 1 comorbidity and at least 20% have 2 comorbidities. The model is already counting in those additional 20% in its equations to estimate comorbidity risk and Life expectancy. These 20% will be double counted when additional factors are implemented to increase the risk further due to multimorbidity factors.

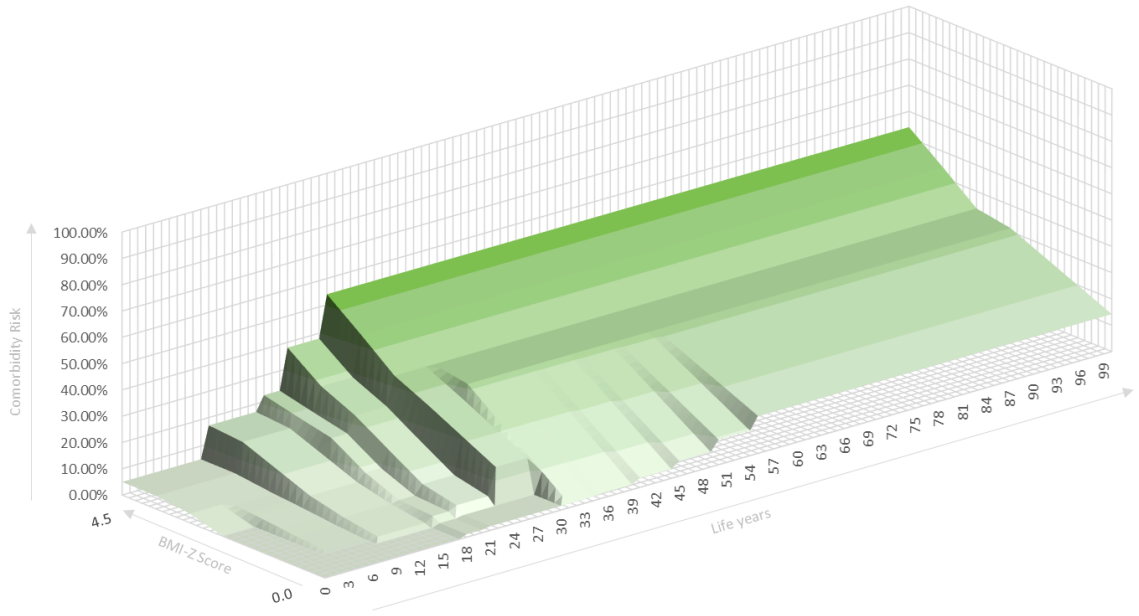
Another capability of the model and one of its main tasks is the assessment of risk reduction resulting from weight loss. Here several dynamics are in play, with the greatest influence on risk reduction being the magnitude of weight reduction. The more weight is reduced, the greater the reduction in the risk of developing comorbidities. Another dynamic of risk reduction is the reduction of obesity duration. by reducing weight at an early stage, the time in which comorbidities can develop due to obesity is reduced, thus a reduction in obesity duration results in a direct decrease in the risk profile. Accordingly, our main finding is that the earlier and more severe you reduce the weight to a healthy level, the greater the risk reduction. This dynamic is influenced by all factors (age, weight, duration) and results in a non-linear progression. For example, the longer you wait to reduce weight, the lower the risk reduction, even if you reduce by the same weight level. This effect is not linear, i.e. the risk reduction is less for each year of delay in weight loss than it was for the previous year.

This is the first and only model to assess the impact of early-onset obesity on mortality and morbidity. It confirms the major impact of early-onset obesity on life expectancy and the benefits of losing weight as early as possible.

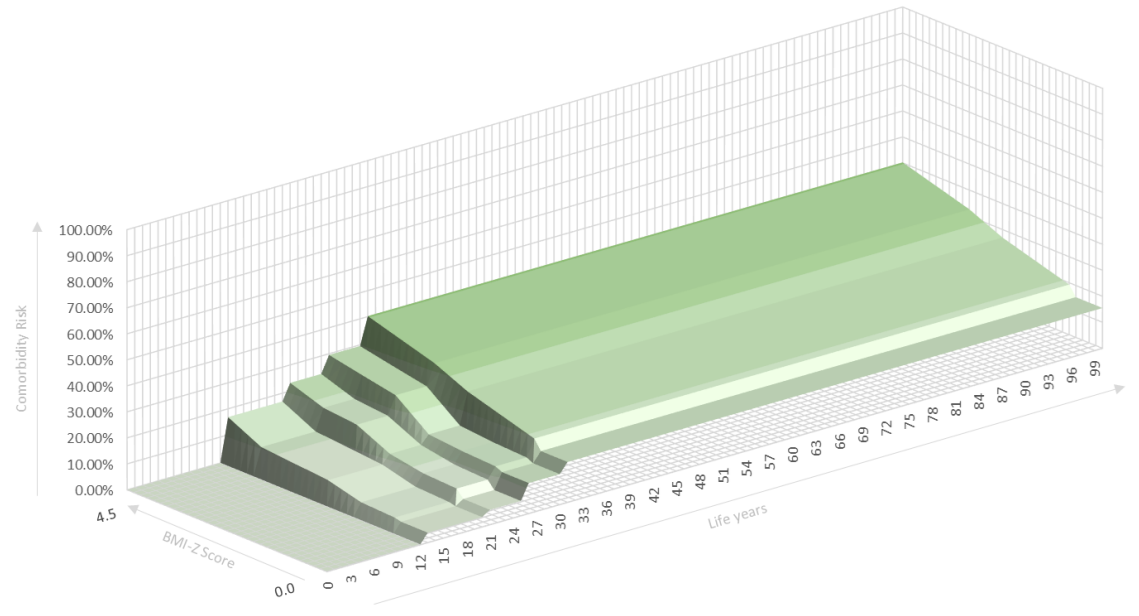
Appendix

Model Graphics

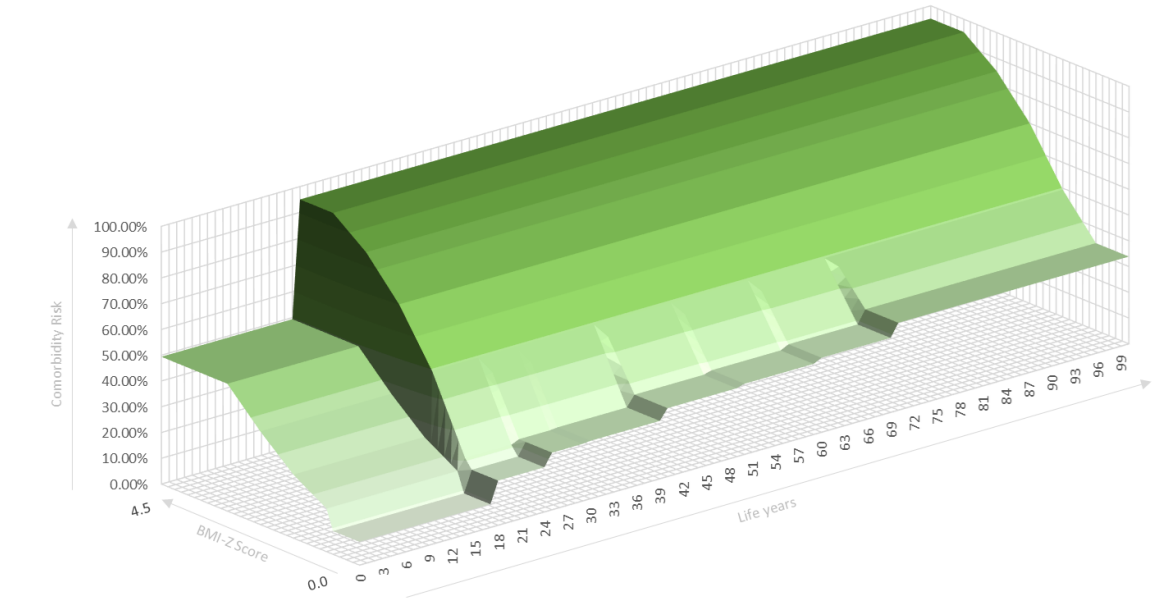
Graphic 1: T2DM Prevalence



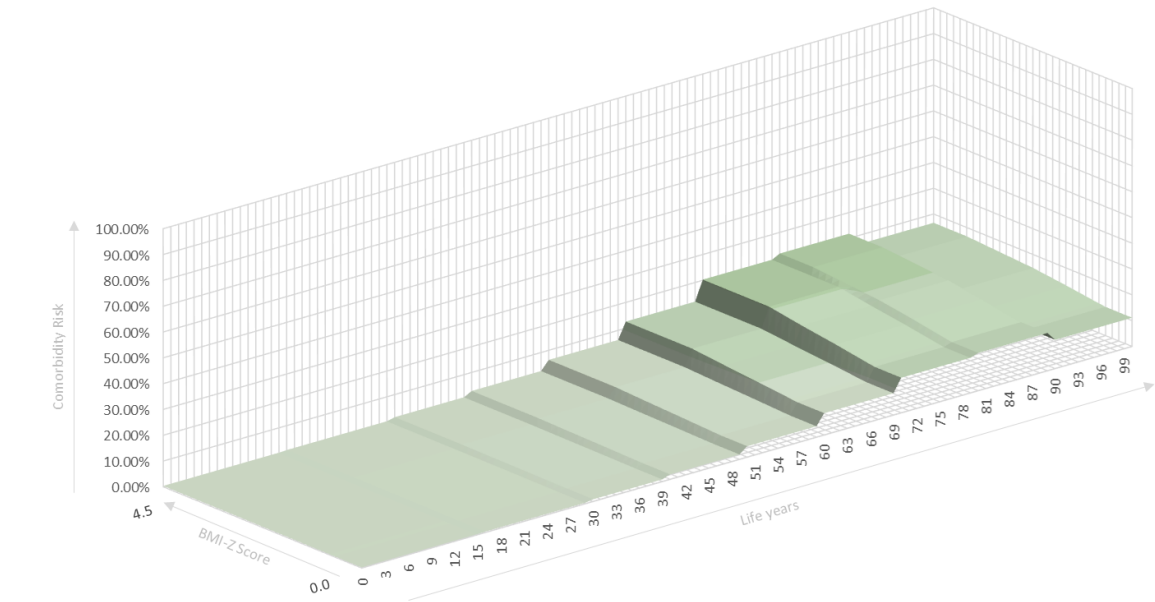
Graphic 2: Cardiovascular Event Prevalence



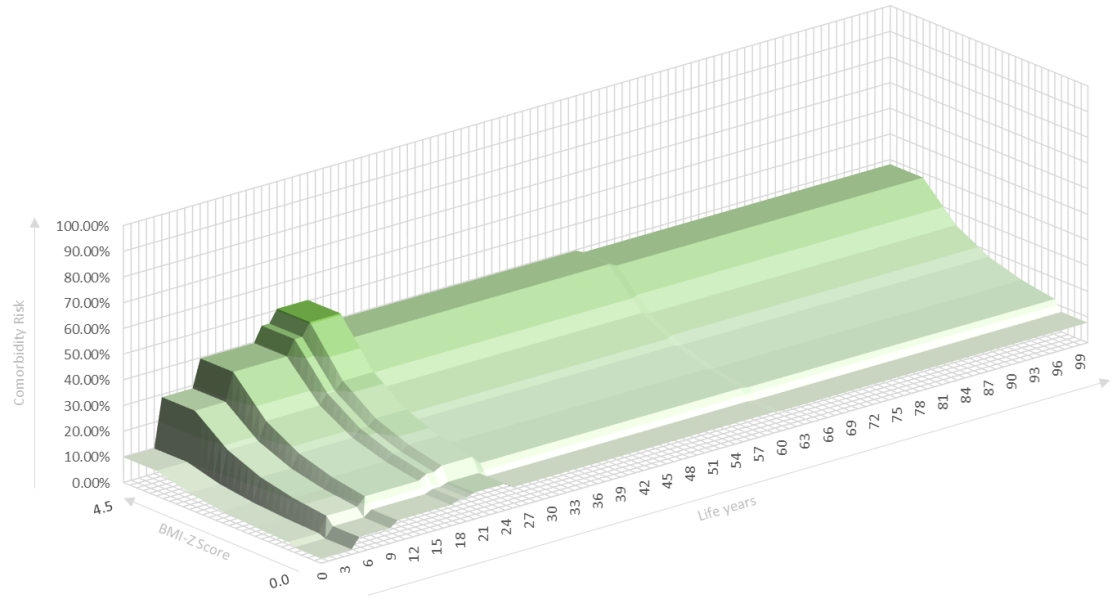
Graphic 3: NAFLD Prevalence



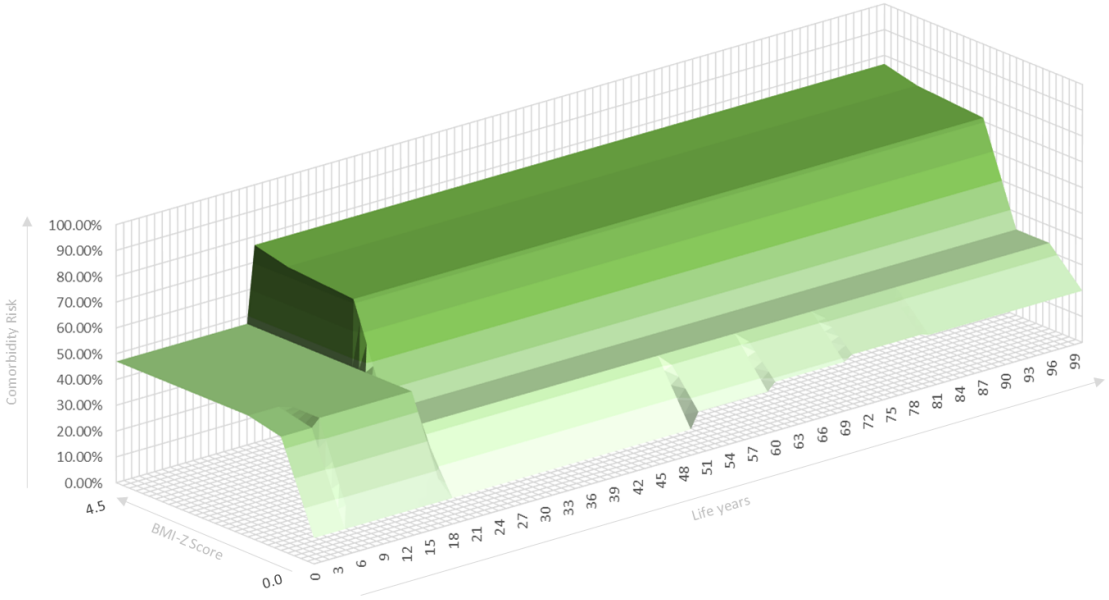
Graphic 4: Cancer Prevalence



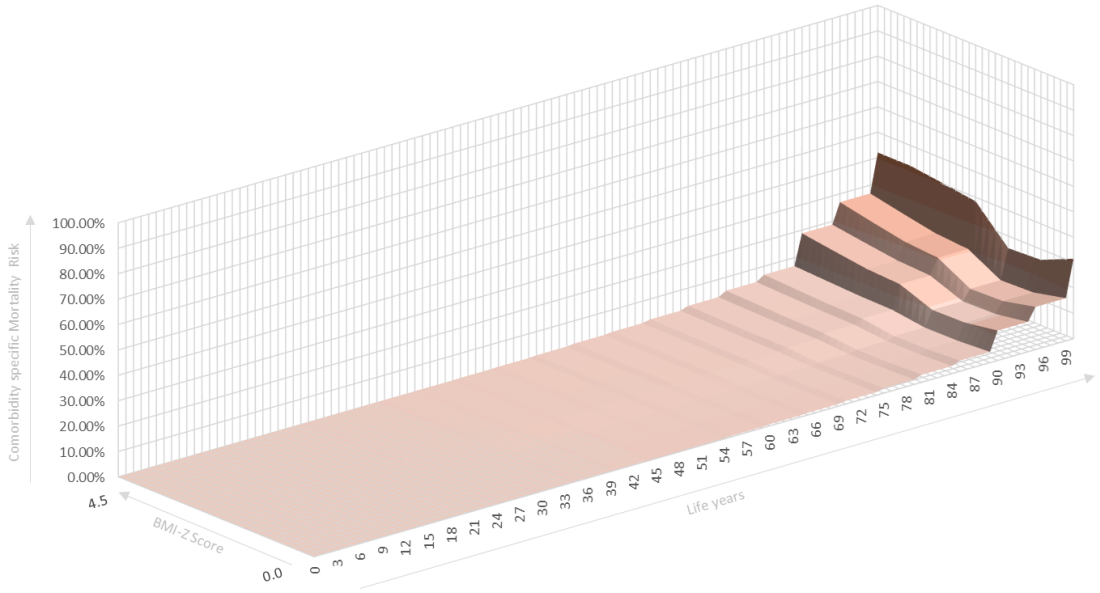
Graphic 5: Asthma Prevalence



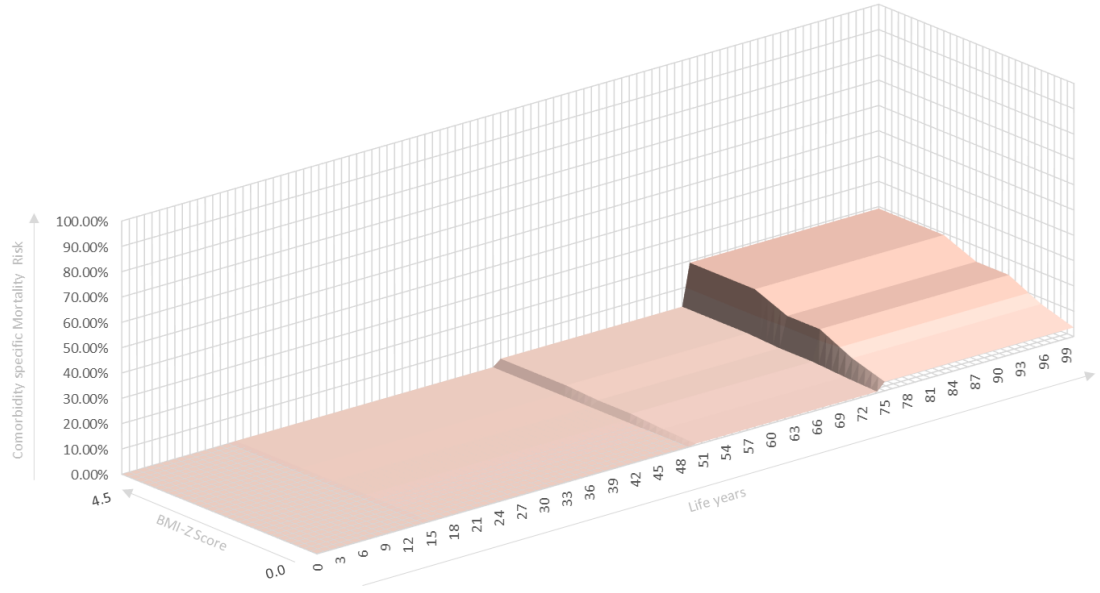
Graphic 6: Sleep Apnea Prevalence



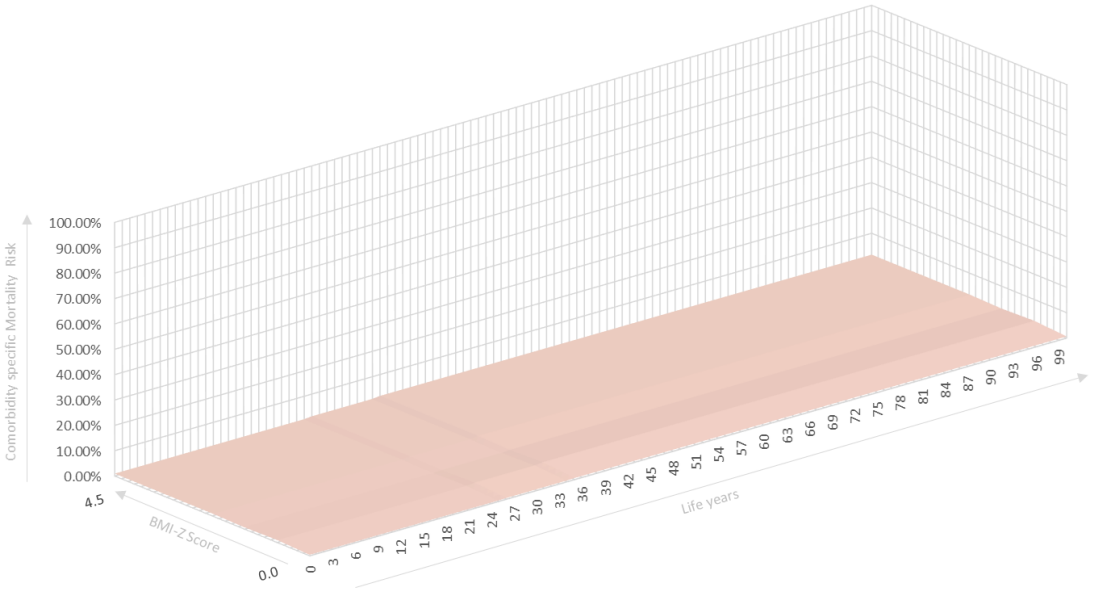
Graphic 7: T2DM Mortality Risk



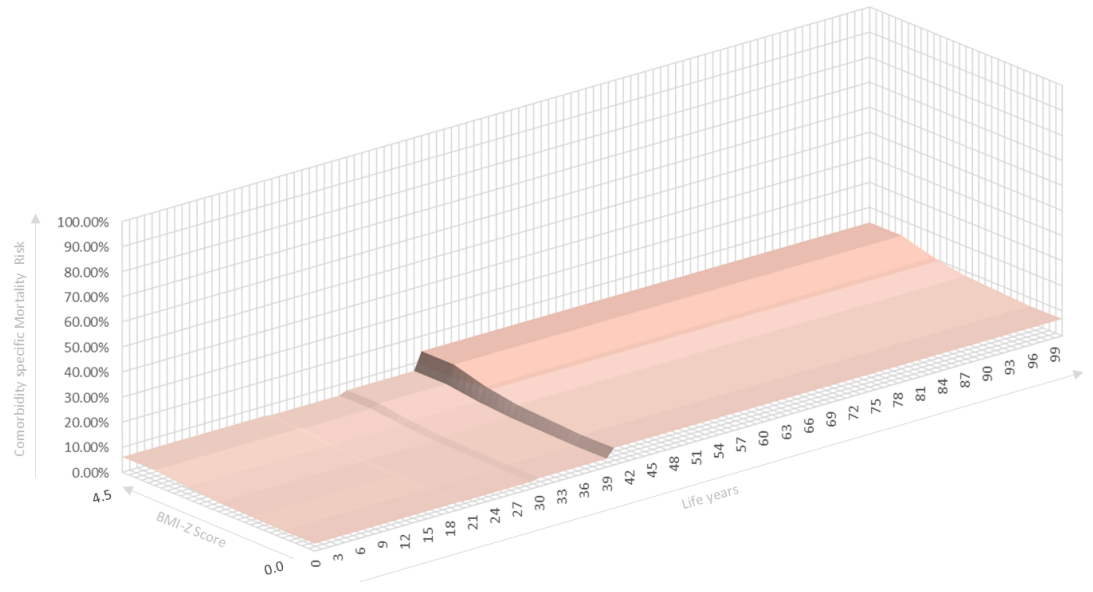
Graphic 8: Cardiovascular Event Mortality Risk



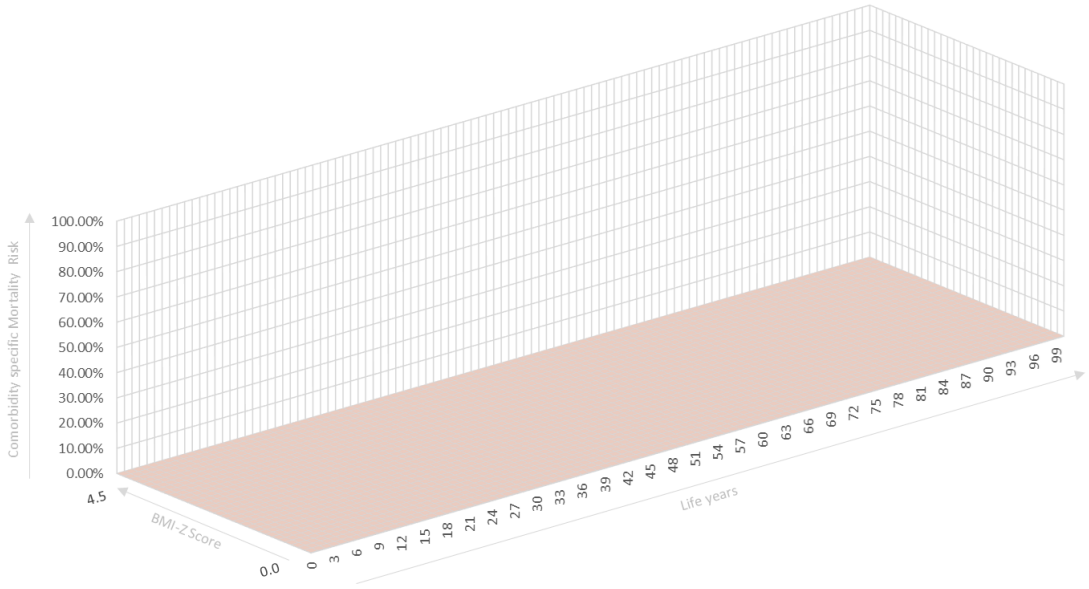
Graphic 9: NAFLD Mortality Risk



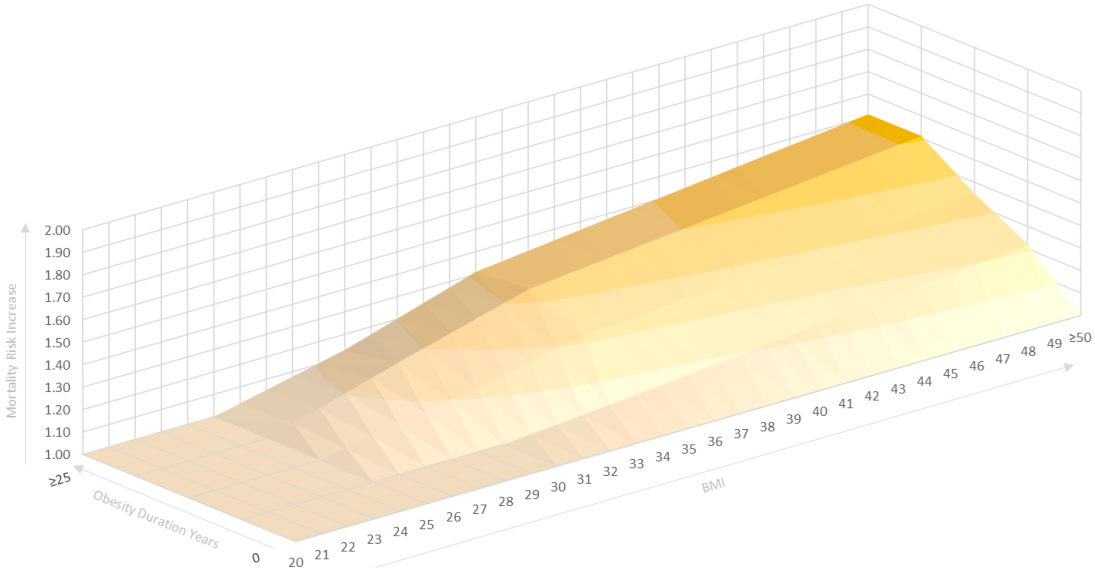
Graphic 10: Cancer Mortality Risk



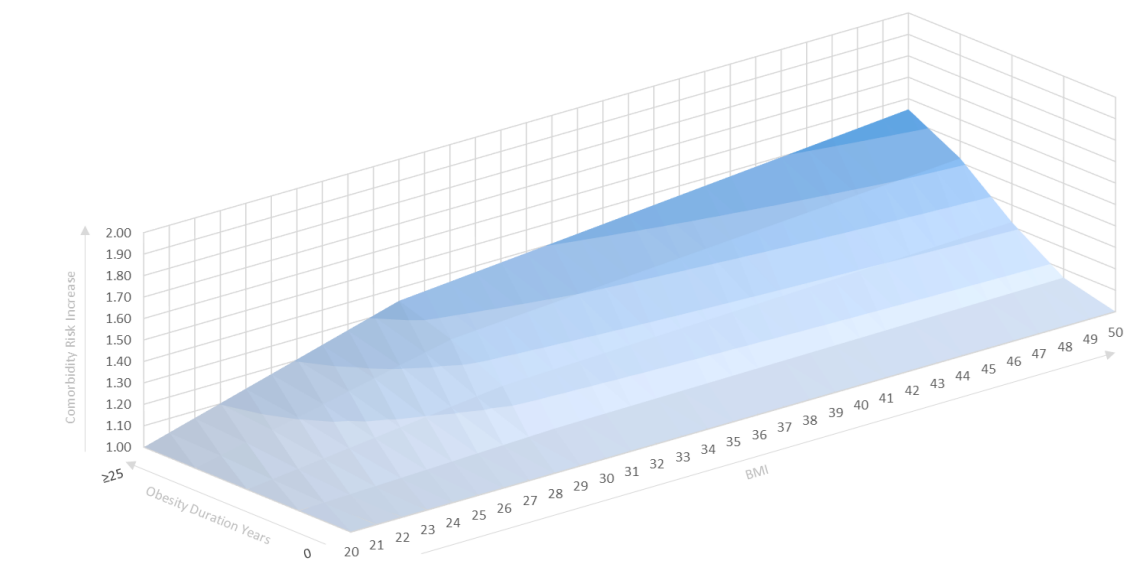
Graphic 11: Asthma Mortality Risk



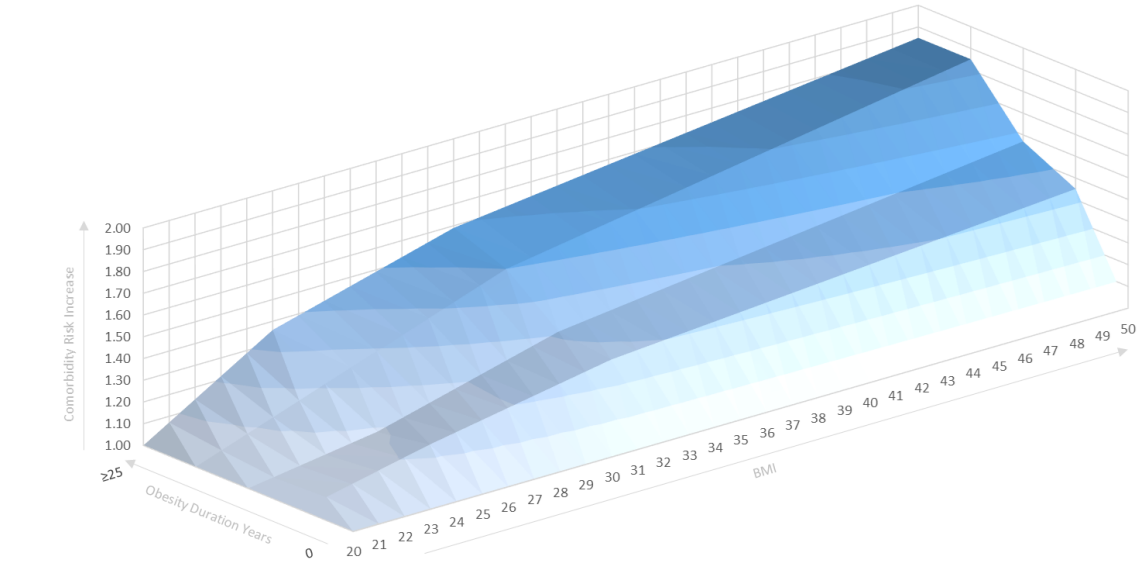
Graphic 12: Obesity Duration impact on Mortality Risk



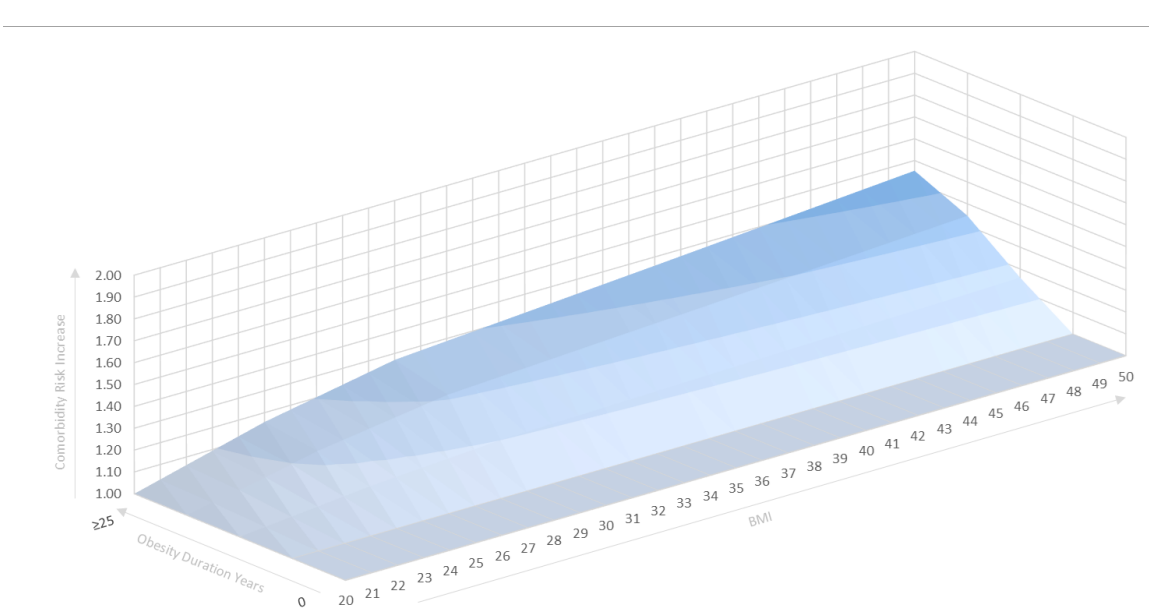
Graphic 13: Obesity Duration impact on T2DM Risk



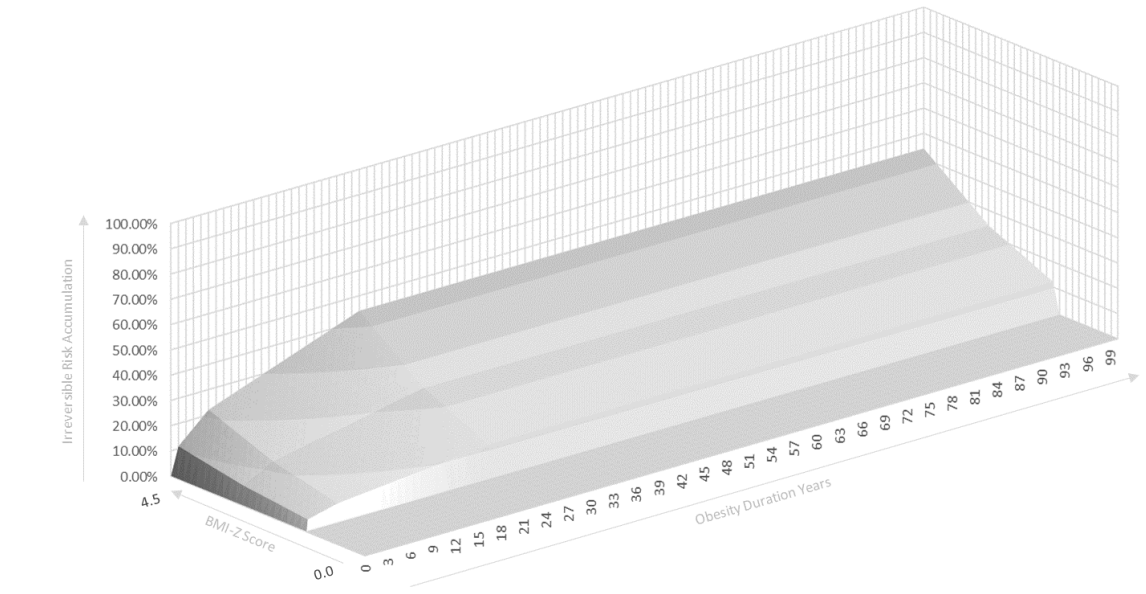
Graphic 14: Obesity Duration impact on Cardiovascular Event Risk



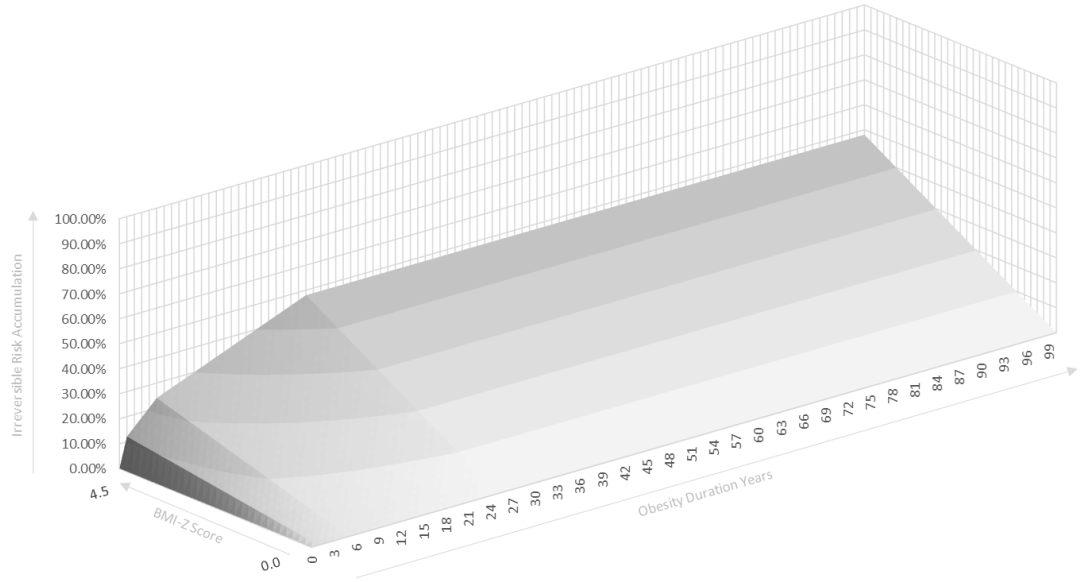
Graphic 15: Obesity Duration impact on Cancer Risk



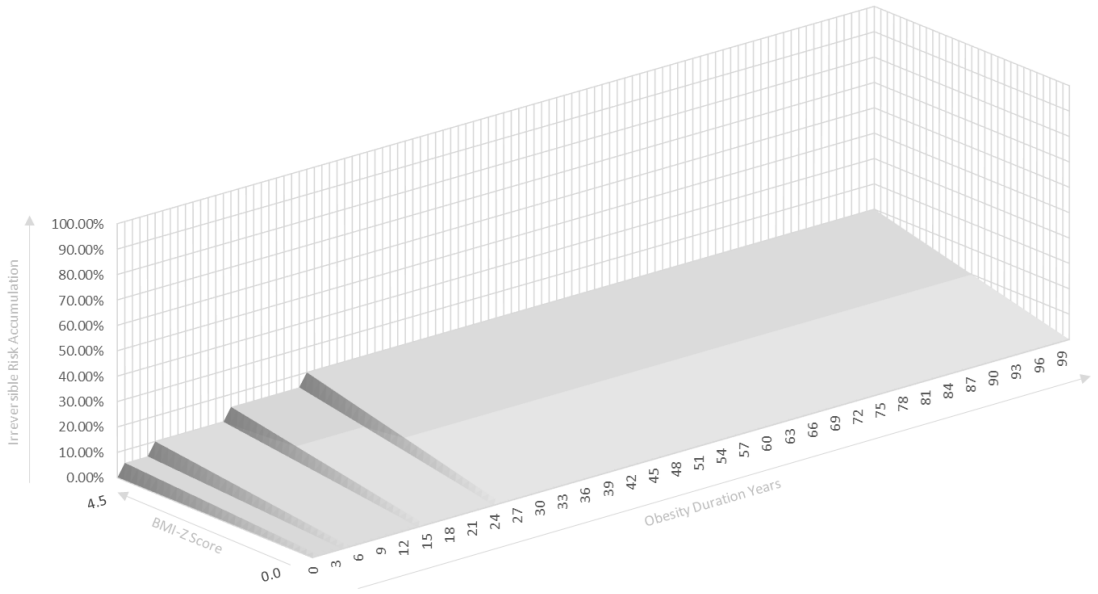
Graphic 16: Irreversible T2DM Risk Accumulation



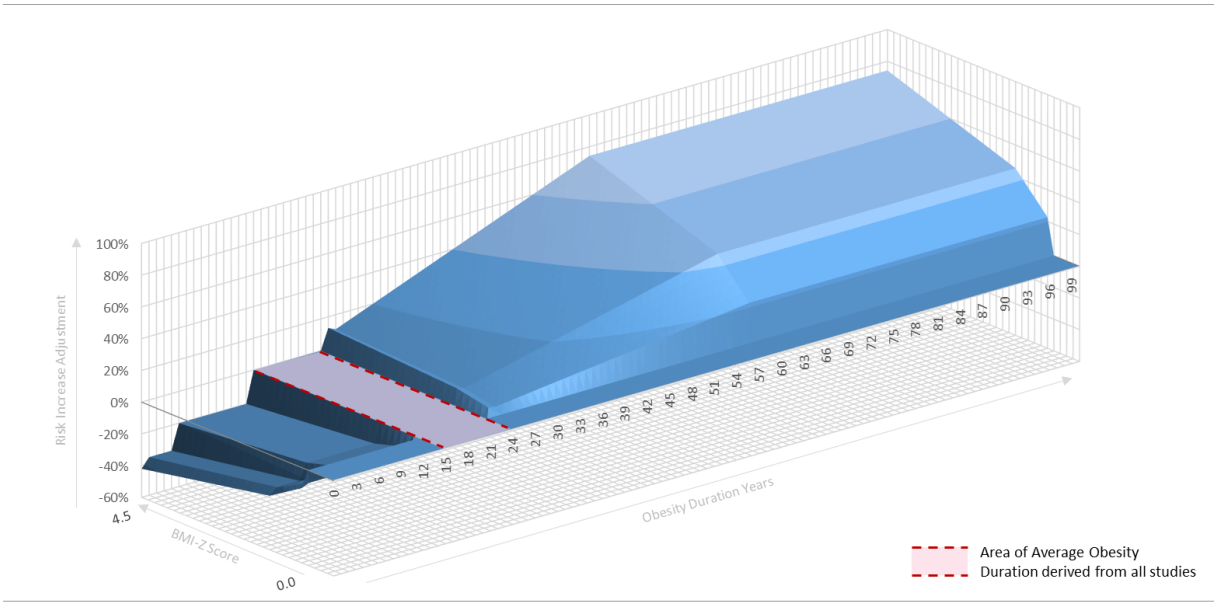
Graphic 17: Irreversible CV Risk Accumulation



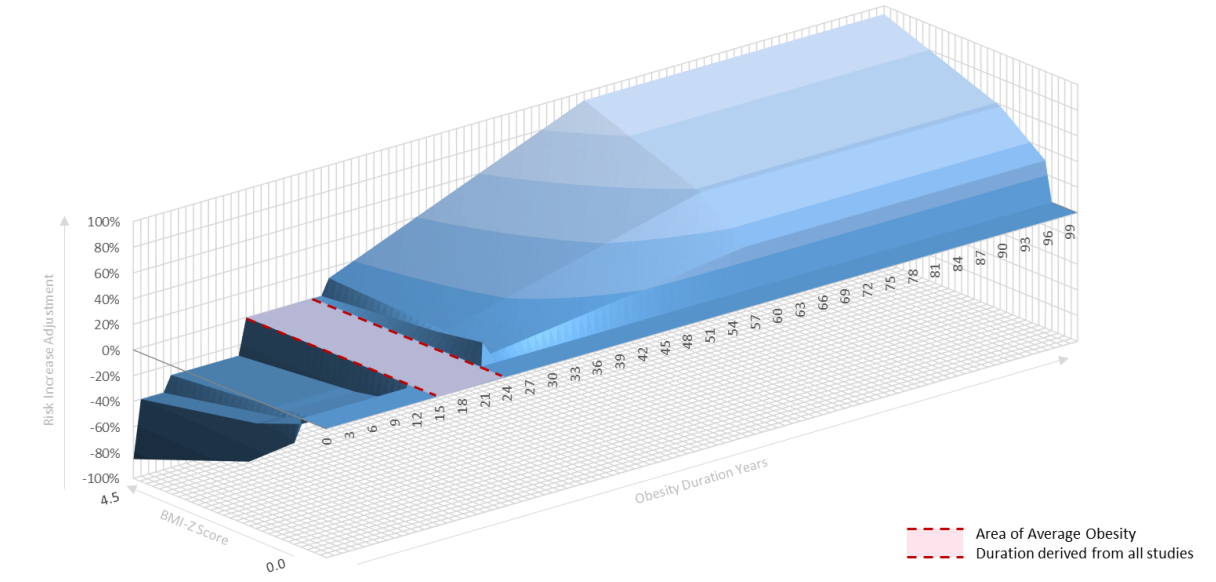
Graphic 18: Irreversible NAFLD Risk Accumulation



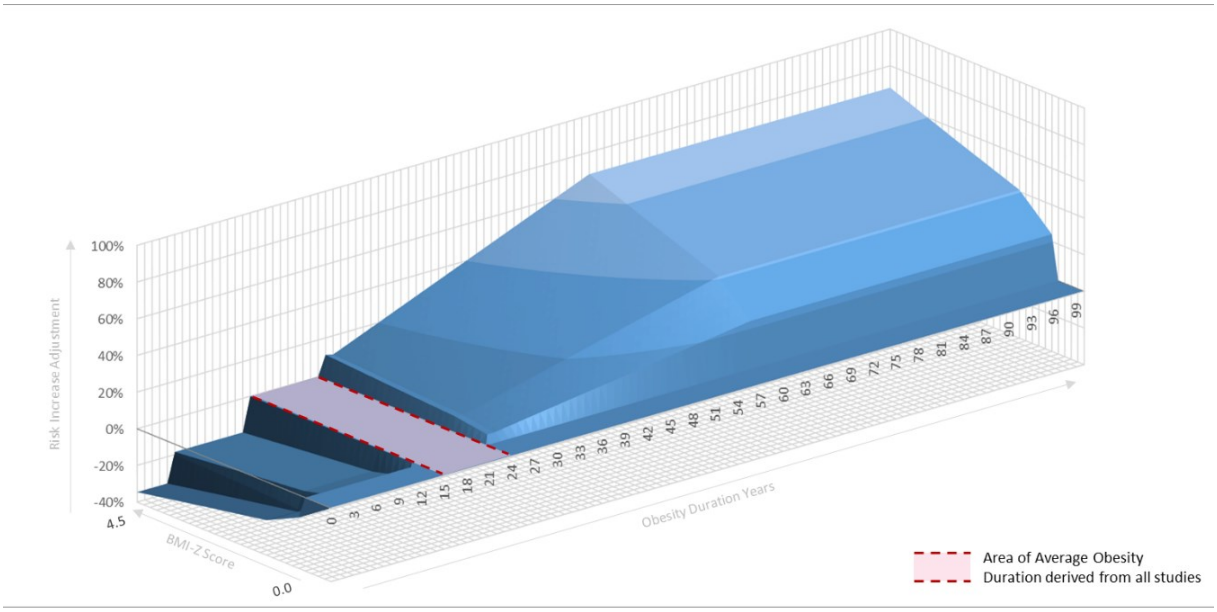
Graphic 19: T2DM Risk adjustment



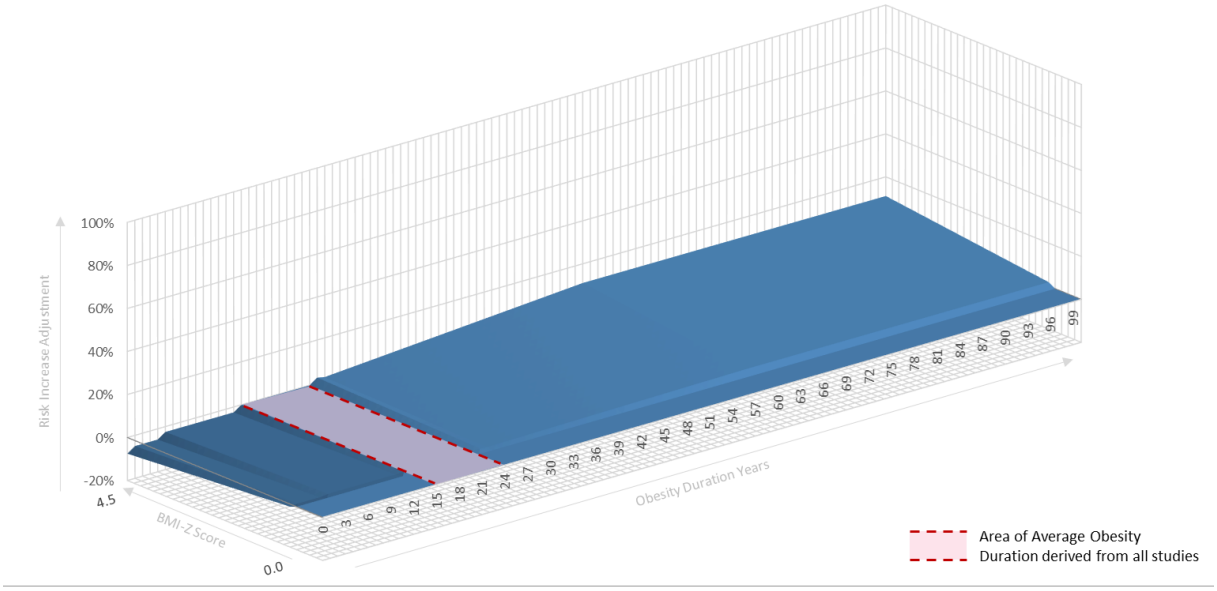
Graphic 20: CV Risk adjustment



Graphic 21: Cancer Risk adjustment



Graphic 22: NAFLD Risk adjustment



Literature Overview

Studies included.

1. Tanamas et al. 2018, Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population
2. Ahmad et al. 2014, Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey
3. Bjerregaard et al. 2018, Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes
4. Carstensen et al. 2020, Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016
5. Salehidoost et al. 2018, Body mass index and the all-cause mortality rate in patients with type 2 diabetes mellitus
6. Mulnier et al. 2005, Mortality in people with Type 2 diabetes in the UK
7. Liu et al. 2019, Cause-Specific Mortality in Multiethnic South East Asians with Type 2 Diabetes Mellitus
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Appendix A - Analysis of data presented in Table 35 of the Company Submission, BMI Z-score shift data for individual BBS patients aged <18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients), considering BMI-Z class intervals of 0.5 and correcting for placebo (based on 2.5% points reduction due to placebo effect)

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean
Placebo contribution to BMI-Z at week 52 (based on 2.5% reduction due to placebo effect)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BMI-z at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BMI-z at week 52 (corrected for placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Difference in BMI-z score (corrected for placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shift in BMI-z class if 0.5 intervals are considered and corrected for placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI-z class intervals changed assuming intervals of 0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

Cost-effectiveness results following draft guidance

This document outlines the updated base-case and scenario analyses results for setmelanotide following the consultation period. These results include the updated simple discount of [redacted]%.

Summary of revised base case assumptions

- A 100% paediatric initiated population
- A baseline population of 75% severe hyperphagia and 25% moderate hyperphagia
- Weighted average of [redacted] & [redacted] BMI-Z class shift [av. Class shift of [redacted]]
- 1% discontinuation rate
- EAG-corrected mapping of BMI-Z PedsQL scores to EQ-5D
- Ongoing weight management monitoring costs
- [redacted] adult caregivers

Table 1 Revised base case and scenario results with updated PAS (probabilistic results)

		Inc. Costs	Inc. QALYs	Inc. Undiscounted QALYs	ICER
Base Case		[redacted]	[redacted]	[redacted]	**£197,588**
Scenario 1	Mixed Population [60% paediatric]	[redacted]	[redacted]	[redacted]	£202,620
Scenario 2	1.56 BMI-Z class shift	[redacted]	[redacted]	[redacted]	£200,089
Scenario 3	2% discontinuation rate	[redacted]	[redacted]	[redacted]	£196,677
Scenario 4	Mapping correction for lit-based EQ-5D	[redacted]	[redacted]	[redacted]	£207,756
Scenario 5	EOObesity-Model mortality and comorbidities	[redacted]	[redacted]	[redacted]	£193,361

Table 2 Two-way threshold analysis for treatment effect on hyperphagia and population at treatment initiation

Undiscounted QALYs; ICER		**Population at treatment initiation**		
		100% severe	**75% severe, 25% moderate**	**60% severe, 40% moderate**
Treatment Effect on Hyperphagia	**Three-class shift for severe; two-class shift for moderate:** • 100% severe to no hyperphagia • 100% moderate to no hyperphagia	[redacted] £163,462	[redacted] £177,708	[redacted] £187,513
	Two-class shift for both severe and moderate: • 100% severe to mild • 100% moderate to None	[redacted] £181,307	[redacted] £193,214	[redacted] £201,139
	BASE-CASE: Two-class shift for Severe; one-class shift for moderate • 100% severe to mild • 100% moderate to mild	[redacted] £181,307	[redacted] £199,001	[redacted] £211,379

Figure 1 Probabilistic sensitivity analysis of incremental cost-effectiveness ratio for setmelanotide in paediatric-initiated patients with BBS

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RESEARCH

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Caregiver burden in Bardet-Biedl syndrome: findings from the CARE-BBS study

Elizabeth Forsythe[1*], Usha G. Mallya[2], Min Yang[3], Caroline Huber[2], Mary Lynn Cala[3], Alexandra Greatsinger[3], Ella Hagopian[3], Jeremy Pomeroy[4] and Andrea M. Haqq[5]

Abstract

Background Bardet-Biedl syndrome (BBS) is a rare, genetically heterogeneous obesity syndrome associated with hyperphagia. Given the early onset of BBS symptoms in childhood and multifaceted complications, this study aimed to quantify the caregiver burden associated with BBS.

Methods A cross-sectional, multi-country survey of caregivers from the United States (US), United Kingdom (UK), Canada, and Germany was designed to quantify the extent of caregiver burden associated with obesity and hyperphagia symptoms (i.e., uncontrollable hunger) among patients with BBS.

Results A total of 242 caregivers across the four countries met the inclusion criteria and completed the survey. The mean (standard deviation [SD]) age of the caregivers was 41.9 (6.7) years, and the mean (SD) age of individuals with BBS in their care was 12.0 (3.7) years. Hyperphagia contributed to a BBS diagnosis in 230 of 242 individuals (95.0%). On average, caregivers used eight different weight management approaches for those in their care and expressed a strong desire for more effective weight management methods. Based on the *Impacts of Hyperphagia: Caregiver version*, patients' hyperphagia had a moderate-to-severe impact on caregiver mood (56.6%), sleep (46.6%), and relationships (48.0%). Caregivers reported experiencing a high level of personal strain (mean [SD], 17.1 [2.9]) and family impact (mean [SD] score, 26.0 [3.8]) due to BBS, as measured by the *Revised Impact on Family Scale*. Among caregivers in the workforce, there also was high impairment in total work productivity (mean [SD], 60.9% [21.4%]) due to caring for patients with BBS according to the *Work Productivity and Activity Impairment*. More than half (53%) of the caregivers reported spending over 5,000 out-of-pocket in local currency for medical expenses for the patient with BBS in their care.

Conclusions Obesity and hyperphagia have negative impacts on the lives of caregivers of patients with BBS. The burden is demonstrated to be multifaceted, with various components that may interact with and confound each other, including intensive weight management efforts, productivity loses, impaired family dynamics and out-of-pocket medical expenses.

Keywords Bardet-Biedl syndrome, Caregiver burden, Hyperphagia, Obesity, Personal strain, Work productivity

*Correspondence:
Elizabeth Forsythe
elizabeth.forsythe@ucl.ac.uk
Full list of author information is available at the end of the article

Introduction

Bardet-Biedl syndrome (BBS) is a rare, genetically heterogeneous syndrome that affects approximately 4000–5000 patients in the United States (US), with an incidence rate of 1:100,000-1:140,000 in North America and 1:125,000-1:160,000 in Europe [1–3]. BBS is a ciliopathy, a class of disorders associated with genetic mutations that result in abnormal formation or function of cilia [4]. As a result, it is characterized by multisystemic clinical features and complications that often begin to appear during childhood, including retinal dystrophy, postaxial polydactyly, obesity, genital anomalies, renal anomalies, and learning disabilities [3, 5]. Severe early-onset obesity and pathological insatiable hunger (hyperphagia) are two key characteristic manifestations of this rare genetic disorder. Based on data from the Clinical Registry Investigating BBS (CRIBBS), 70% of patients with BBS have obesity relative to only 20% of the general population [6, 7].

Historically, obesity associated with BBS has been treated symptomatically with a focus on the management of diabetes, hypertension, and metabolic syndrome to delay the onset of secondary complications among these patients [5, 8]. Given the negative effects of obesity and hyperphagia on health and quality of life, weight management and control of hyperphagia are two of the key goals for patients with BBS. However, this is challenging because caregivers must implement strict environmental controls, such as supervising children around food, securing food sources, reducing energy intake, and adhering to meal schedules [6]. While controlling caloric intake, these strategies often fail to address the persistent underlying hyperphagia [6].

The hyperphagia attributes associated with BBS, particularly food-seeking behavior, are often characterized as relentless and overwhelming and can result in a substantial burden on families and caregivers that negatively affects their well-being [9]. Caregivers may also be at risk of potentially increased isolation from their communities and/or feelings of loneliness due to the all-consuming need to care for the patient, and the social stigmatization of having a child dealing with obesity and abnormal food seeking behaviors. The net impact of this burden translates to impaired work productivity, and an increased financial burden [10, 11]. However, the challenges facing caregivers and families of patients with BBS in everyday life are not well-quantified, which impairs the development of optimal strategies to sustain caregivers in their vital roles of supporting patients with BBS. To that end, this survey study, CARE-BBS (CAREgiver Burden in Bardet-Biedl Syndrome), aimed to quantify the extent of the physical, emotional, and financial toll on caregivers providing care for patients with BBS.

Methods

Study population

A cross-sectional, multi-country survey was designed to collect data from adult caregivers of patients with BBS who live with obesity and hyperphagia. Caregivers were recruited from the US, United Kingdom (UK), Canada, and Germany through a market research panel if they cared for a patient with BBS for ≥ 6 months and were able to read and understand the local language of their country. Participating caregivers were required to complete a short screener to confirm they met the study inclusion and exclusion criteria. Inclusion criteria were all caregiver-reported and included the patient having BBS and obesity. The obesity criteria could be met via caregiver-reported the patient currently having obesity or ever having a weight in the ≥ 95th percentile for the patient's age and sex. Professional caregivers (i.e., those paid for their time to care for the patient with BBS) and caregivers of patients who were enrolled in a clinical trial at the time of the survey or during the preceding 6 months were excluded from the study. Caregivers who provided informed consent and met all inclusion criteria were invited to complete the full survey and received an honorarium for their time to complete the survey. This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments and was granted an exemption from a full review by the US Pearl Independent Review Board.

Survey components

The survey was designed to collect information on patient characteristics as well as caregivers' sociodemographics, medical history, and burden of caregiving. Specifically, caregiver burden was characterized across several domains, including the impact of caregiving on the caregiver's professional work and productivity, activities of daily life, physical and mental health, and financial stress, specifically with regards to financial costs associated with patients' medical care, weight management, and caregiver-reported expenses related to patient care. The specific measures are as follows:

Impacts of hyperphagia© (IoH): caregiver version

The newly developed *Impacts of Hyperphagia: Caregiver version* contains 5 items measuring the impact of hyperphagia on the daily life of the caregiver regarding sleep, mood/emotions, work, leisure/recreational activities and relationships using a 4-point agreement scale ("Not at all", "A little", "Moderately", "A great deal"). An overall score was generated by summing the scores across all items

with a score range from 0 to 15, where higher scores indicate greater impacts of hyperphagia.

Work productivity and activity impairment (WPAI)–obesity associated with BBS: caregiver

The WPAI questionnaire was adapted to measure the impact of caregiving on productivity (e.g., hours missed from work and actual hours worked) and impairment on work and regular activities due to caregiving for someone with BBS. The WPAI has 6 items and a recall period of "the past 7 days." Items 5 and 6 that measure impacts on work and impairment of activities utilize an 11-point numeric rating scale (NRS) (0 "Health problem has no effect on my work/daily activities" to 10 "Health problem completely prevented me from working/doing my daily activities"). The WPAI produces 4 scores based on the following outcomes: absenteeism (percentage of work time missed), presenteeism (percentage of impairment while working, total productivity impairment (percentage of overall work impairment), and total activity impairment (percentage of activity impairment). Scores range from 0–100% whereby a higher percentage indicates greater work or activity impairment [12].

Patient-reported outcomes measurement information system® (PROMIS) scale v1.2–global health: adult

The PROMIS Scale v1.2–Global Health has 10 items assessing an adult's overall health. This instrument generates a Global Mental Health score and a Global Physical Health score. All items except one use 5-point Likert scales (5 "Excellent" to 1 "Poor"; 5 "Completely" to 1 "Not at all"; 5 "Never" to 1 "Always", and 5 "None" to 1 "Very severe"). One item that measures pain is on an 11-point NRS whereby 0 represents "No pain" and 10 represents "Worst pain imaginable". A T-score was calculated using response pattern scoring; a higher T-score represents better overall health. T-scores can range between 16.2 and 67.7 for physical health and 21.2–67.6 for mental health [13].

Revised impact on family scale© (RIOFS)

The RIOFS has 15 items assessing a family member's perception of the effect of a patient's chronic condition on family life. The instrument has been shown to have strong face validity and favorable psychometric evaluations, including construct validity [14]. The RIOFS generates a total score using a 4-point Likert scale ("Strongly Agree", "Agree", "Disagree", "Strongly Disagree") whereby higher scores indicate that the patient's chronic condition has a greater impact on family life.

Other measures assessed in the CARE-BBS study included the Symptoms of Hyperphagia: Caregiver Version, the PROMIS Parent Proxy Scale v1.0—Global Health, and the IWQOL-Kids: Parent-Proxy, which are reported elsewhere as they are beyond the scope of the current analysis.

Statistical analyses

Data were pooled across the four countries, and the demographic and medical history of caregivers were described overall and by country. Responses underwent a quality check to assess internal logic and quality of responses, and responses that failed to meet quality checks were excluded from analyses. Instruments were scored, including the total score and domain scores, where applicable, and descriptively summarized overall and by country. Given the early onset of BBS symptoms in many patients, the WPAI questionnaire and PROMIS Scale outcomes were stratified by the age of the patient with BBS (age groups: < 6, 6–11, 12–17, 18 +) to understand if the age of the patient with BBS had a differential impact on caregivers' ability to work and their general health. Means and standard deviations (SDs) were reported for continuous variables, while counts and percentages were reported for categorical variables. R 3.6.3 (R Core Team, 2020) was used for all data analyses.

Results

Study population characteristics

The final study sample included a total of 242 caregivers who met the eligibility criteria, completed the survey, and passed quality checks, among whom 60 were from the US, 59 were from the UK, 62 were from Canada, and 61 were from Germany. Two caregivers who met the inclusion criteria but failed the quality check due to logically inconsistent responses were excluded from the analysis. The median (SD) age of caregivers was 41.9 (6.7) years with 54% male, and 93% being a parent of the patient (52% being the father and 42% being the mother). The majority of caregivers were married or in a domestic partnership (86%). Nearly all caregivers (98%) reported that there was another person assisting with caregiving responsibilities, most often another parent (73%). Caregivers generally reported being in good health, with a small proportion having an eating disorder, anxiety, high blood pressure, high cholesterol, or a sleep disorder (all < 10%). More than 80% reported having household income ≥ 75,000 in local currency. Caregiver characteristics were generally similar across country of residence, though Germany had a notably higher proportion of male participants (62.3%) and a slightly lower proportion of participants who reported being married or in a domestic partnership (78.7%) than other countries (Table 1).

Table 1 Demographics and Medical History of Caregivers by Country

	Overall N = 242	Canada N = 62	Germany N = 61	UK N = 59	US N = 60
Demographics					
Age (years), mean ± SD (median)	41.9 ± 6.7 (42)	42.9 ± 6.7 (42)	42.1 ± 7.7 (43)	40.1 ± 7.9 (41)	42.4 ± 3.6 (43)
Sex, n (%)					
Male	131 (54.1)	29 (46.8)	38 (62.3)	34 (57.6)	30 (50.0)
Female	111 (45.9)	33 (53.2)	23 (37.7)	25 (42.4)	30 (50.0)
Married or in a domestic partnership, n (%)	209 (86.4)	52 (83.9)	48 (78.7)	52 (88.1)	57 (95.0)
Highest education attainment (top 4), n (%)					
High school diploma/equivalent or lower	16 (6.6)	1 (1.6)	12 (19.7)	3 (5.1)	-
Some college/university or Associate's degree	56 (23.1)	20 (32.3)	12 (19.7)	17 (28.8)	7 (11.7)
College or university graduate/bachelor's degree	107 (44.2)	27 (43.5)	25 (41.0)	25 (42.4)	30 (50.0)
Advanced degree	63 (26.0)	14 (22.6)	12 (19.7)	14 (23.7)	23 (38.3)
Household income (in local currency), n (%)					
< 75,000	33 (13.6)	5 (8.1)	17 (27.9)	10 (16.9)	1 (1.7)
≥ 75,000	208 (86.0)	57 (91.9)	43 (70.5)	49 (83.0)	59 (98.3)
Prefer not to say	1 (0.4)	-	1 (1.6)	-	-
Relationship to person with BBS, n (%)					
Mother	101 (41.7)	30 (48.4)	21 (34.4)	20 (33.9)	30 (50.0)
Father	125 (51.7)	28 (45.2)	34 (55.7)	33 (55.9)	30 (50.0)
Other	16 (6.6)	4 (6.5)	6 (9.8)	6 (10.2)	-
Others responsible for care of person with BBS, n (%)					
Parent	176 (72.7)	43 (69.4)	46 (75.4)	46 (78.0)	41 (68.3)
Grandparent	29 (12.0)	7 (11.3)	10 (16.4)	7 (11.9)	5 (8.3)
Other	32 (13.2)	8 (12.9)	9 (14.8)	7 (11.9)	8 (13.3)
No others are responsible	43 (17.8)	10 (16.1)	11 (18.0)	8 (13.6)	14 (23.3)
Medical History					
Currently receiving treatment for condition (top 5), n (%)					
Eating disorders	19 (7.9)	1 (1.6)	4 (6.6)	11 (18.6)	3 (5.0)
Anxiety disorders	13 (5.4)	1 (1.6)	4 (6.6)	3 (5.1)	5 (8.3)
High blood pressure	12 (5.0)	1 (1.6)	5 (8.2)	3 (5.1)	3 (5.0)
High cholesterol	12 (5.0)	2 (3.2)	2 (3.3)	3 (5.1)	5 (8.3)
Sleep disorders	10 (4.1)	4 (6.5)	2 (3.3)	2 (3.4)	2 (3.3)

BBS: Bardet-Biedl Syndrome; SD: standard deviation

The mean (SD) age of patients with BBS was 12.0 (3.7) years, with 63% between ages 12 and17 and 64% males. The mean (SD) time since BBS diagnosis was 4.2 (2.8) years, and obesity and hyperphagia contributed to a BBS diagnosis in the majority of the patients (95%). The majority (85%) of patients in the sample were considered to have obesity at the time of the survey (95th percentile or above for pediatric patients, and BMI of 30 or higher for adult patients), followed by being overweight (11%) (pediatric patients in the 85th to < 95th percentile, or BMI of 25 to < 30 for adult patients); 10 patients (4%) were considered to have normal weight. About a third (38%) of caregivers reported that a genetic test related to BBS was performed on the patient with BBS, and almost two-thirds (63%) of these caregivers reported that a mutation was found in the test results. Patient characteristics were similar across country of residence.

Direct impacts due to patients' hyperphagia

On average, caregivers reported employing eight strategies at the time of the survey to manage the weight of the patient with BBS (Additional file 1). The average number of strategies reported was similar across country of residence, with a maximum average number of strategies of 8.8 in the US and a minimum of 7.4 average strategies in the UK. While caregivers reported satisfaction with existing weight management approaches (mean (SD) score of 7.4 (1.6) on a scale of 0 "lowest satisfaction" to

10 "highest satisfaction"), they felt that having new effective approaches to manage weight was highly important (mean (SD) score of 7.8 (1.4) on a scale of 0 "lowest importance" to 10 "highest importance").

The majority of caregivers (~90%) reported that the patient's hyperphagia had at least some negative impact on the caregiver's sleep, mood/emotions, work, leisure activities and/or relationships with family or friends. Around half of caregivers reported the impact was "moderate" or "a great deal" in the following domains: sleep over the past 7 days (57%), mood or emotions (57%), work (53%), leisure or recreational activities (53%), and relationships with family or friends (48%). More caregivers in the UK reported an impact on sleep over the past 7 days (71%), and fewer caregivers in Canada reported an impact on work (34%) and on relationships with friends and family (29%) versus the overall caregiver sample (Table 2).

Impacts on ability to work and general health

Since they started caring for a patient with BBS, more than half the caregivers reported that it affected their ability to work, including 20% who reduced their work hours, 19% who temporarily stopped working or went on leave, and 15% who permanently stopped working or retired early. Results were heterogenous across countries. Compared to the overall sample, a higher proportion of UK caregivers reported having to switch jobs (9% vs. 18%), temporarily stop working (19% vs. 29%) and reduce work hours (20% vs. 29%), while a higher proportion of German caregivers reported early retirement (20%; Additional file 2). Three-quarters (76%) of caregivers reported working at the time of the survey: 59% were full-time employees, followed by 14% who were part-time employees and 5% who were self-employed (Additional file 3). Caregivers who were working at the time of the survey reported substantial

Table 2 IoH© – Caregivers by Country

	Overall N = 242	Canada N = 62	Germany N = 61	UK N = 59	US N = 60
Average summary scale scores (Range: 0–15) mean ± SD	7.8 ± 3.2	6.5 ± 2.5	7.8 ± 3.4	8.7 ± 3.5	8.4 ± 2.7
During the past 7 days to what extent did the person in your care's hunger negatively affect your…					
Sleep? n (%)					
Not at all	23 (9.5)	9 (14.5)	5 (8.2)	2 (3.4)	7 (11.7)
A little	82 (33.9)	22 (35.5)	25 (41.0)	15 (25.4)	20 (33.3)
Moderately	94 (38.8)	26 (41.9)	21 (34.4)	26 (44.1)	21 (35.0)
A great deal	43 (17.8)	5 (8.1)	10 (16.4)	16 (27.1)	12 (20.0)
Mood or emotions? n (%)					
Not at all	28 (11.6)	9 (14.5)	9 (14.8)	6 (10.2)	4 (6.7)
A little	77 (31.8)	25 (40.3)	15 (24.6)	17 (28.8)	20 (33.3)
Moderately	97 (40.1)	23 (37.1)	24 (39.3)	26 (44.1)	24 (40.0)
A great deal	40 (16.5)	5 (8.1)	13 (21.3)	10 (16.9)	12 (20.0)
Work? n (%)					
Not at all	33 (13.6)	10 (16.1)	9 (14.8)	7 (11.9)	7 (11.7)
A little	80 (33.1)	31 (50.0)	19 (31.1)	14 (23.7)	16 (26.7)
Moderately	92 (38.0)	20 (32.3)	23 (37.7)	27 (45.8)	22 (36.7)
A great deal	37 (15.3)	1 (1.6)	10 (16.4)	11 (18.6)	15 (25.0)
Leisure or recreational activities? n (%)					
Not at all	34 (14.0)	11 (17.7)	11 (18.0)	8 (13.6)	4 (6.7)
A little	80 (33.1)	22 (35.5)	19 (31.1)	17 (28.8)	22 (36.7)
Moderately	81 (33.5)	22 (35.5)	23 (37.7)	15 (25.4)	21 (35.0)
A great deal	47 (19.4)	7 (11.3)	8 (13.1)	19 (32.2)	13 (21.7)
Relationships with family or friends? n (%)					
Not at all	40 (16.5)	15 (24.2)	7 (11.5)	10 (16.9)	8 (13.3)
A little	86 (35.5)	29 (46.8)	23 (37.7)	17 (28.8)	17 (28.3)
Moderately	83 (34.3)	18 (29.0)	21 (34.4)	17 (28.8)	27 (45.0)
A great deal	33 (13.6)	-	10 (16.4)	15 (25.4)	8 (13.3)

IoH: Impacts of Hyperphagia; SD: standard deviation

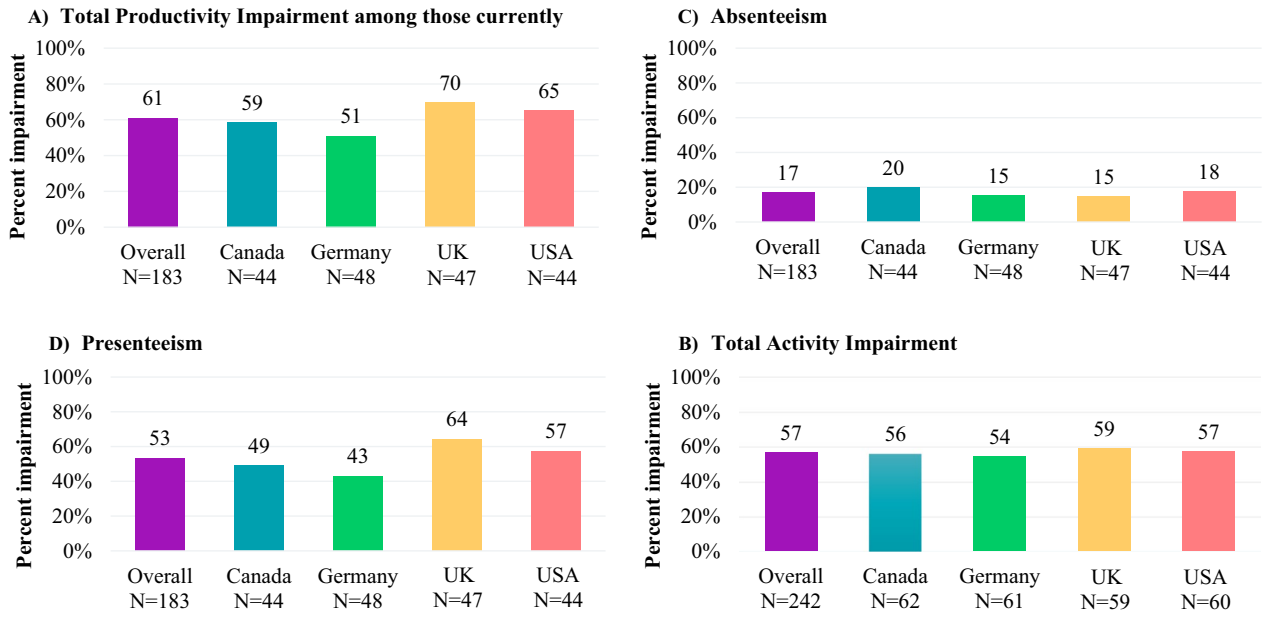

Fig. 1 WPAI—BBS Caregiver by Country (Range: 0–100%). BBS: Bardet-Biedl Syndrome; WPAI: Work Productivity and Activity Impairment

impairment in productivity on the WPAI questionnaire, with an average total productivity impairment of 61%, absenteeism of 17%, and presenteeism of 53%; the total activity impairment was also substantial at 57%. The extent of total productivity impairment and presenteeism were highest among caregivers in the UK (70% and 64%) and lowest among caregivers in Germany (51% and 43%, respectively; Fig. 1). When

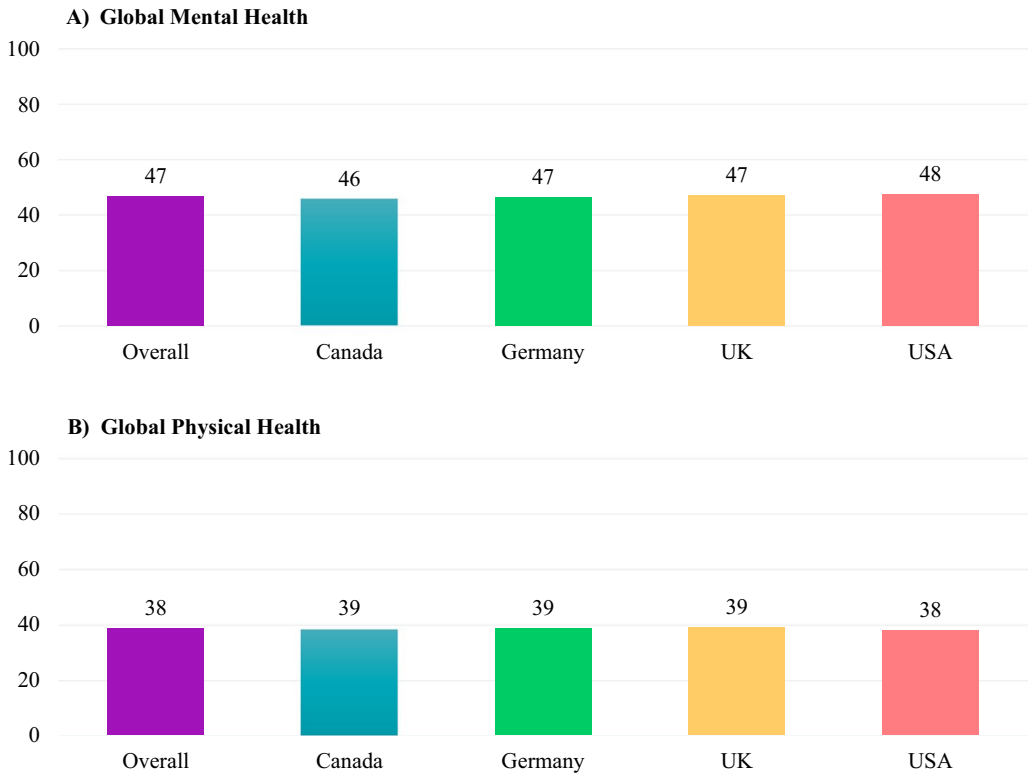

Fig. 2 PROMIS® Scale—BBS Caregiver by Country. BBS: Bardet-Biedl Syndrome; PROMIS: Patient-Reported Outcomes Measurement Information System

stratified by patient age, caregivers of patients in the < 6 and 6–11 age groups reported being most impacted as it related to their ability to work and perform regular daily activities.

Though caregivers reported a mean (SD) score of 46.8 (6.5) regarding their own mental health on the PROMIS Scale, which is comparable to the general population, they reported poorer physical health with a mean (SD) score of 38.4 (3.5; Fig. 2). Nearly half (49%) of the caregivers considered their overall health to be "very good" or "excellent", and a similar proportion (48%) considered they carried out their usual social activities and roles "very good" or "excellent." Self-rated overall and mental health PROMIS scores were similar across countries.

When stratified by patient age, the PROMIS Global Mental Health score for caregivers was lowest for those who cared for patients in the < 6 and 18 + age groups, with mean (SD) ratings of 42.6 (6.8) and 44.0 (7.0), respectively. Mental health ratings of caregivers were slightly better in the 6–11 and 12–17 age groups, with mean (SD) scores of 48.3 (6.4) and 46.5 (6.4), respectively. The PROMIS Global Physical Health score stratified by patient age was consistently relatively low in the 6–11, 12–17, and 18 + age groups, with average ratings of 38–39.

Impacts on family

The financial burden due to medical care of patients with BBS was substantial. More than half (53%) of the caregivers reported spending over 5000 out-of-pocket in local currency for medical expenses over the past 12 months; 36% reported spending 1001–5000 out-of-pocket (Fig. 3). Over half (53%) the caregivers reported the financial burden associated with caring for a patient with BBS as "catastrophic" (3%), "significant" (22%), or "moderate" (29%; Fig. 4). Study participants considered BBS to have a moderate-to-high family and social impact as evidenced by an average total RIOFS score of 43 (possible score range: 15–60), with an average personal strain score of 17 (possible score range: 6–24) and an average familial/social impact score of 26 (possible score range: 9–36). Average total impact, personal strain, and familial/social impact scores were similar across countries (Fig. 5).

Discussion

This cross-sectional survey helps to fill an important gap in the literature by being the first to quantify the burden of caregivers for patients with BBS across four countries and document that this burden is multifaceted and can increase financial strain and barriers to professional work among caregivers, particularly caregivers of young children with BBS. Caregiver responses were mostly similar across countries, although there was some heterogeneity given the differences of the healthcare systems and the extent of availability and accessibility of social supports across countries. Of note, caregiver country of origin was not collected in the survey, which could have an impact on the perception and hence reporting of the burden. Nonetheless, given the rarity of BBS, previous evidence on caregiver burden has been limited to small sample sizes; to that effect the current study makes a novel contribution to the field via its comparably large sample size [10, 11].

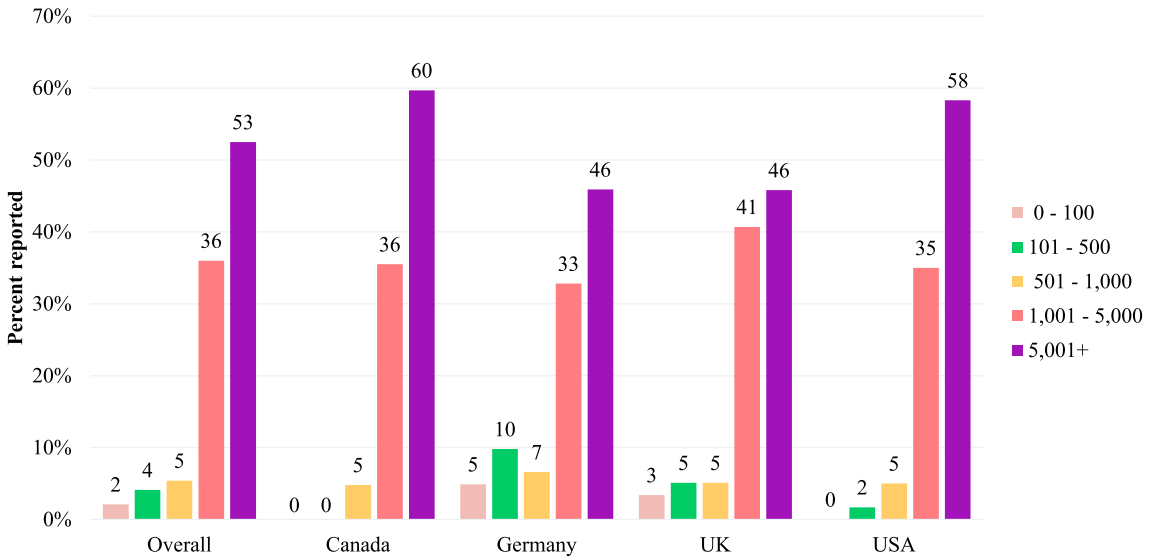

Fig. 3 Out-of-Pocket Medical Expenses for Patients with BBS over the Past 12 Months by Country in Local Currency. BBS: Bardet-Biedl Syndrome

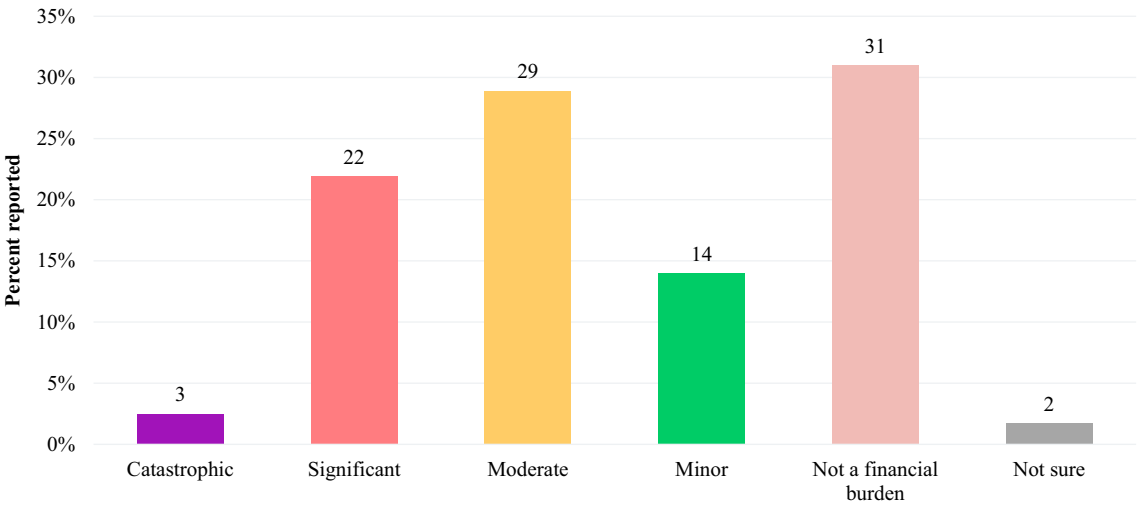

Fig. 4 Financial Burden of Caring for Patients with BBS. BBS: Bardet-Biedl Syndrome

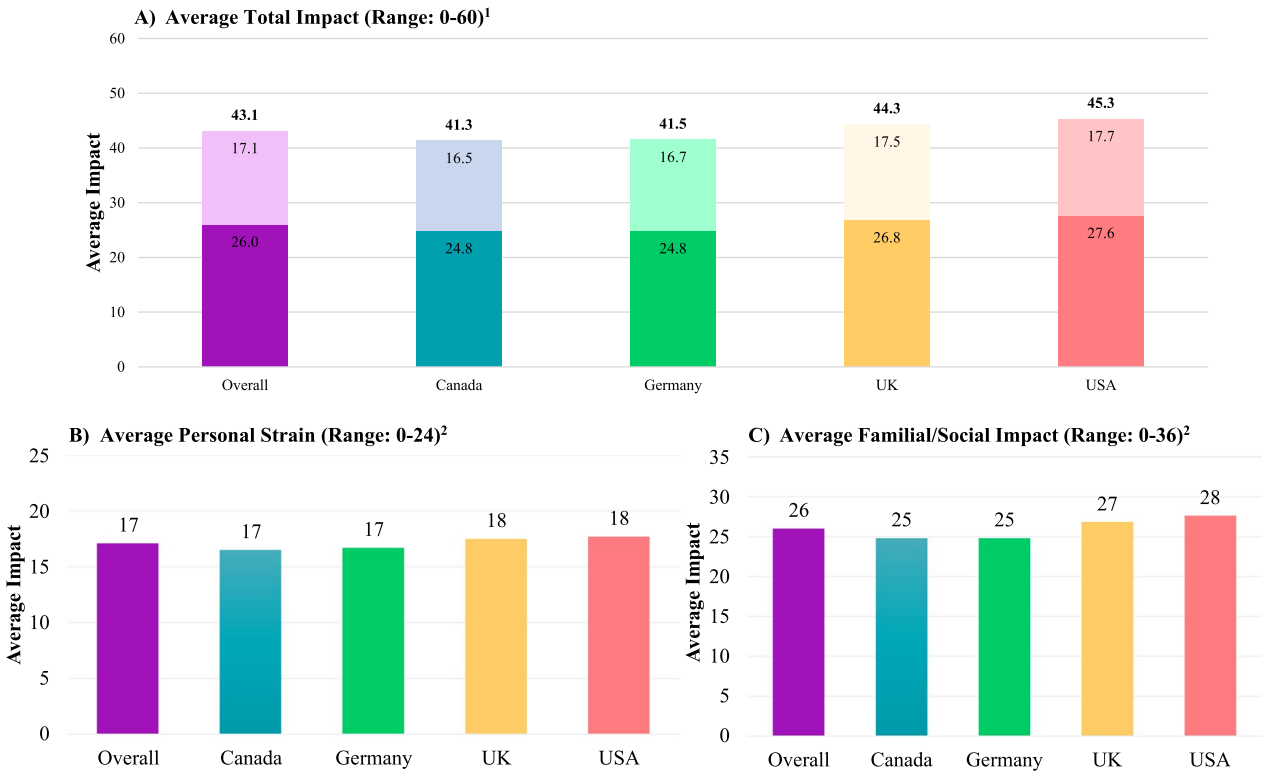

Fig. 5 Revised IOFS by Country. BBS: Bardet-Biedl Syndrome; IOFS: Impact on Family Scale. 1. Higher scores indicate that BBS has a greater impact on the family. The bottom bars (dark colors) correspond to the average Familial/Social Impact scores (Range: 0–36) and the top bars (light colors) correspond to the average Personal Strain scores (Range: 0–24). The bolded number at the top of each stacked bar corresponds to the average Total Impact scores (Range: 0–60). 2. Higher scores indicate that BBS has a greater impact on the family

These study results substantiate prior qualitative work that found obesity and hyperphagia have a negative impact on the lives of patients with BBS, their caregivers, and their families [15]. One prior interview study of parents of children with BBS found that these parents often experienced distress due to poor awareness of BBS among people in their lives, including healthcare professionals, and the difficulty of coordinating with multiple

services to support caretaking activities [10]. Other studies have shown that caregivers of young children with early-onset obesity and BBS often experienced negative social judgment or blame due to their association with a person who was overweight or had obesity, which is an example of weight bias and courtesy stigma [16–18]. A 2015 qualitative study of 28 parents of children with BBS illustrated the impact of such negative social perceptions, as participants reported feeling blamed, devalued and judged by others for their child's obesity, which resulted in recurrent emotions of anger, frustration, and helplessness among parents [11]. The CARE-BBS study adds to the insight from these studies through a quantification of caregiver burden and its associated negative impacts.

In particular, the IoH and PROMIS questionnaires included in the current study were used to further delineate the negative impacts that caregiving can have on the mental and physical health of caregivers. Results indicate that caregivers experience negative impacts in multiple areas of their lives, including sleep, mood, and emotions. In the current study, caregivers reported a high personal strain and strain on their family, underscoring the substantial and widespread socio-emotional cost of managing obesity and hyperphagia that is characteristically associated with BBS. The reduction in physical and mental wellbeing seen in this study population appears comparable to the burden of caregivers for patients with Prader-Willi syndrome, the most frequently diagnosed cause of syndromic obesity, which is also characterized by severe hyperphagia and associated obesity [19, 20]. These findings suggest that high stress and negative mental and physical consequences of caregiving for patients with severe hyperphagia and obesity such as Prader-Willi syndrome and BBS are common and could result in caregiver burnout, compromising their ability to care for the patient and themselves and leading to further emotional exhaustion and family disruption [21, 22].

The impact of obesity and hyperphagia among patients with BBS on caregiver work productivity and the financial burden related to the costs of medical care and affiliated out-of-pocket expenses was found to be substantial in this study. At an average age of 42 years, caregivers who participated in this study are in their prime age for income-earning (the peak ages are 35 to 44 years as reported by the US Bureau of Labor Statistics) [23]. Caregivers who suffer productivity losses during this key earnings time therefore may further face meaningful income setbacks compared to peers who do not endure similar productivity losses. Caregivers in the current study reported the need to reduce their work hours or quit their jobs altogether, as well as having less productivity and more absenteeism, which reflects the efforts required in providing care to patients with BBS over time and the negative impact it can have on the caregivers' quality of life. Similar rates of work loss, either temporarily or permanently, were reported among caregivers of those with fragile X syndrome, the world's most common hereditary cause of intellectual disability [24]. Furthermore, in the 2020 study by Zelihic et al. [10], parents of children with BBS whose workplaces promoted support and coping strategies and enabled fellowship for caregivers reported reduced feelings of isolation within this community. Together with prior research, these findings emphasize the importance of raising awareness of BBS among the general public and healthcare professionals along with strengthening communities and support systems available for caregivers of patients with BBS. Further research is needed to better understand how the availability of different healthcare systems and social support across countries might impact caregiver burden in BBS.

It is worth noting that as a ciliopathy, BBS is a complex condition. Our study focused on quantifying caregiver experiences associated with managing patients' obesity and hyperphagia; however, the extent of efforts that caregivers putting to support their patients are much greater, for example, due to problems with vision loss, diabetes, renal anomalies, etc [3–5]. There is currently a dearth of literature on burden of caregiving for patients with BBS, other ciliopathies, or syndromes with similar manifestations in hyperphagia and obesity. Our study intended to illuminate the unmet needs related to managing obesity and hyperphagia of patients with BBS. However, this may only represent a portion of the caregiving tasked to these families. For example, one study that characterized burden of caring for children with Joubert syndrome and related disorders (JS/JSRD) found that feeling overwhelmed, physical strain, and family adjustment were the most challenging aspects of caregiving among parents of children with JS/JSRD [25, 26].

Though not a ciliopathy, Prader Willi syndrome is another rare multi-system genetic disorder characterized by obesity and hyperphagia. A study on caregivers of those with Prader-Willi syndrome found that the intensity of hyperphagia was associated with the level of burden that caregivers experiences and patients' anxiety and behavioral issues further intensified caregiver burden [18] Two studies on caregivers of patients with Prader-Willi syndrome identified challenges arising from intellectual disabilities and higher unplanned healthcare resource use and costs including managing symptoms such as respiratory distress [18, 26].

On the other hand, our study found that the mental health scores of the caregivers were comparable to the general population on the PROMIS Scale. Additionally, though with an overall worse physical health than the

general population, about half rated their physical health as good or very good. In fact, only 5% of the caregivers reported a diagnosis of anxiety disorder and less than 5% had depression. Inconsistent findings on mental health of the caregivers of children with rare genetic conditions have been observed in the literature. There was a similar finding in the study of caregivers of children with JS/JSRD: while highly distressed, the majority of the caregivers were not clinically depressed and caregiver burden was not related to disease severity of the children, but rather to parents' coping skills and level of family functioning [25]. On the contrary, studies assessing the burden among caregivers of patients with Duchenne muscular dystrophy found that the levels of self-reported anxiety and depression were high and were significantly associated with health status of the patients perceived by the caregivers [27, 28]. We speculate that the extent of the burden perceived by the caregivers could be highly subjective given the nature of these rare genetic conditions, the resources available to the families and family dynamics. A high proportion of our study participants had relatively high levels of education, income, and were married or in a domestic partnership. These factors may have contributed to a generally better health status of the participants in our study, and hence our study could have underestimated the true burden of caregiving. Additionally, despite the obvious challenges in caring for a patient with a rare disease, caregivers may have implemented coping mechanisms and taken action to improve their own lives and the lives of the patients they care for, including joining advocacy groups or engaging research activities that may help make a difference for the lives of these children [29]. Further research is much needed to have a full appreciation of the burden and impacts on the lives of the caregivers of patients with rare genetic conditions such as BBS.

Limitations

A few limitations are to be noted while interpreting the findings from our study. First, all information collected was caregiver-reported, and the reported diagnoses of BBS, obesity, and hyperphagia were not clinically validated. Second, this one-time cross-sectional caregiver survey represents a snapshot in time and cannot be used to draw conclusions about how the burden of caregiving may change over time. A longitudinal study can be valuable to further assess the cumulative burden of the disease or quantify the improvement over time should novel treatments for managing hyperphagia become available. Third, the caregivers taking part in the study were a part of a patient/caregiver panel and may have been more enthusiastic or have more available resources than those who are not involved in such panels. For example, most caregiver participants in our study were college educated (~70% with a Bachelors' or advanced degree) and a higher income than the household average (>80% with a median household income of ≥75,000 in the local currency). It is likely that caregivers with higher incomes/education have more resources available to them to access the needed care support of their patients. Those caregivers who do not have a comparable level of socioeconomic status could encounter additional challenges that are not well reflected in our study. Further research is needed for an in-depth understanding of the full burden of caregiving. Fourth, this study could be subject to selection bias in that only caregivers of patients with BBS who also had obesity and hyperphagia were recruited, although this does represent the large majority of patients with BBS. Finally, the study focused on caregiver burden associated with managing their patients with hyperphagia and obesity. As noted earlier, BBS is a complex medical condition and hence our findings do not reflect the additional burden encountered by the caregivers, for example, caregivers' effort in caring for other medical aspects of the patients given the BBS's multifaceted manifestations, and their ability to provide care for the rest of their family.

Conclusions

This survey conducted across the US, UK, Canada, and Germany is the first to quantify the multifaceted burden of caregivers of patients with BBS, including the daily management of hyperphagia and weight control, caregivers' ability to work, direct impact on families, and financial strain. These findings provide important information that improves our understanding of how caregivers are impacted while caring for patients with BBS who are suffering from obesity and hyperphagia and highlight the substantial needs for effective interventions to alleviate symptoms and improve the quality of life of patients and their caregivers.

Abbreviations

BBS	Bardet-Biedl syndrome
BMI	Body mass index
CARE-BBS	Caregiver burden in Bardet-Biedl syndrome
CRIBBS	Clinical registry investigating Bardet-Biedl syndrome
IoH	Impacts of hyperphagia©
IRB	Independent review board
IWQOL	Impact of weight on quality of life
JS/JSRD	Joubert syndrome and related disorders
NRS	Numeric rating scale
PROMIS	Patient-reported outcomes measurement information system®
RIOFS	Revised impact on family scale©
SD	Standard deviation
UK	United Kingdom
US	United States
WPAI	Work productivity and activity impairment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-023-02692-8.

Additional file 1. Number of Weight Management Approaches by Country.

Additional file 2. Caregiver Employment Changes by Country.

Additional file 3. Caregiver Current Employment by Country.

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Author contributions
UGM, MY, CH, MLC, AG and EH contributed to study design, data collection, data analysis and interpretation, and critical review of the manuscript. EF and JP contributed to data interpretation and critical review of the manuscript. AMH contributed to the study design, data interpretation, and critical review of the manuscript. MLC was an employee of Analysis Group at the time of the study. All authors read and approved the final manuscript.

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Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was provided by the US Pearl Independent Review Board (IRB) under the Exempt category.

Consent for publication
Not applicable.

Competing interests
EF has received consulting fees from Rhythm Pharmaceuticals, Inc.; participated in the BBS advisory board for Rhythm Pharmaceuticals, Inc.; and is a clinical investigator for clinical trials of setmelanotide in Bardet-Biedl syndrome for Rhythm Pharmaceuticals, Inc. UGM and CH are employees of Rhythm Pharmaceuticals, Inc. and receive stock or stock options with Rhythm Pharmaceuticals, Inc. MY, AG, and EH are employees of Analysis Group, Inc., which received funding to conduct this study. MLC is a former employee of Analysis Group, Inc., which received funding to conduct this study. JP receives research support from Rhythm Pharmaceuticals, Inc. as a co-investigator for the Setmelanotide Phase 2 Treatment of Obesity in Rare Genetic Disorders (ClinicalTrials.gov Identifier NCT03013543) and as a co-investigator of a study examining unmet medical needs related to obesity in people with Bardet-Biedl syndrome. AMH receives grant funding from the Weston Family Microbiome Initiative and Canadian Institutes of Health Research, is a member of the BBS advisory board for Rhythm Pharmaceuticals, Inc., is a member of the 2021–2022 Somatrogon advisory board for Pfizer, Inc., and is a clinical investigator for trials with Rhythm Pharmaceuticals, Inc. and Levo Therapeutics.

Author details
[1]University College London Great Ormond Street Institute of Child Health, London WC1N 1EH, UK. [2]Rhythm Pharmaceuticals, Inc., Boston, MA, USA. [3]Analysis Group, Inc., Boston, MA, USA. [4]Marshfield Clinic Research Institute, Marshfield, WI, USA. [5]Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada.

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Publisher's Note

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 24 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bardet-Biedl Syndrome UK (BBS UK)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the evaluation stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	August 2022: Rhythm Pharmaceuticals provided £7,000 sponsorship to the BBS UK conference in September 2022 to contribute to running costs of the meeting. June 2023: Rhythm Pharmaceuticals provided £10,000 sponsorship to the BBS UK conference (September 2023) to contribute to running costs of the meeting. Rhythm had no influence over the creation, development or content of the meeting.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted], [redacted], BBS UK

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Thank you for the opportunity to provide feedback on the evaluation committee decision. We are disappointed that setmelanotide, the only treatment under review for hyperphagia in BBS, has not been approved at this time, however are hopeful that NICE and the Company can work through the issues raised. We are grateful to the Committee for the consideration they have given to this appraisal, we understand the difficulties involved in the decision-making,

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	particularly when the condition is so rare and there are many unknowns that have to be considered. We have certainly felt the responsibility of being the only patient organisation for Bardet-Biedl syndrome in the UK, however we hope that our close relationship to our community enabled us to effectively relay the experience of living with BBS and the devastating impact of hyperphagia in our submission.
2	We note there is ambiguity regarding the level of hyperphagia before and after taking setmelanotide. As we have shown in our submission, living with hyperphagia is extremely life-limiting for those affected, its impact is felt across the whole family, and it places an excessive additional burden of care on the primary care-giver; there is no reprieve. BBS patient expert, D, provided the following statement for this response: “Hyperphagia whether it’s moderate or severe, it’s still there no matter what the severity, and severely impacts on BBS patient’s lives and their families and caregivers. I didn’t feel the impact was fully considered in the meeting and the focus was on it being moderate or severe - whatever the severity, the drug would still stop the hyperphagia and would change the lives of BBS patients for the better and would improve health levels as well. I know this as I experienced being on the drug and it changed my life”. Reducing hyperphagia, even marginally, will reduce the impact and burden for the patient, carer and wider family and it is worth re-stating that BBS patients are also affected by emotional and communication difficulties, anxiety, low mood and depression, which exacerbates the impact of hyperphagia and ability to cope and vice versa.
3	We appreciate the recognition that setmelanotide should be used in addition to best supportive care with dietary and exercise interventions. The promotion of healthy eating and exercise is embedded in BBS UK’s culture, however maintaining a healthy diet and exercise regime is extremely difficult for those with hyperphagia and obesity, as reported in our submission. The approval of setmelanotide would give BBS patients the support needed to successfully take control of their eating and wellbeing, promoting positive outcomes for their physical and mental health.
4	We would like to finish by reiterating our thanks to all involved in the appraisal of setmelanotide. We understand the complexity of the issues raised, however we trust that considering the significant potential that this treatment brings for improved quality of life outcomes, for the patient, carer and family, that there is enough will and expertise on both sides to reach a positive conclusion. As has

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	been noted, there is no comparable treatment for hyperphagia and it is therefore unthinkable that those living with this devastating condition will be denied access to this treatment. To that end, BBS UK are keen to engage with and support the Company and Committee in any way needed to ensure a positive outcome for this appraisal process.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Obesity and Metabolic Surgery Society

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	It is stated that “Hunger generally increases after surgery” meaning bariatric surgery. There is clear evidence that there is appetite control with bariatric surgery with both huger reduction and increase in satiety in patients without BBS. There are no studies examining formally hunger after

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	bariatric surgery in patients with BBS. Patients with BBS may not have the same respond to bariatric surgery as patients with BBS.
2	As bariatric surgery is rarely used for BBS, it is understandable not to include bariatric surgery as a comparator.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
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- Do not use abbreviations.
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Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG Response to Company Comments on Draft Guidance Consultation

Produced by: Bristol Technology Assessment Group, University of Bristol

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Declared competing interests of the authors: None of the Bristol TAG authors have any conflicts of interest to declare.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

[redacted]

1 ABBREVIATIONS

Abbreviation	Definition
BBS	Bardet-Biedl syndrome
BMI	Body Mass Index
BMI-Z	Body Mass Index Z score
EAG	Evidence Assessment Group
HRQoL	Health-Related Quality of Life
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
PAS	Patient Access Scheme
PedsQL	Paediatric Quality of Life Inventory
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

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2 INTRODUCTION

This report provides the evidence assessment group (EAG) review of the additional analyses, and results provided by Rhythm Pharmaceuticals (company) in response to the draft guidance consultation for Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome. The company has provided an updated base-case, scenario analyses, and has updated its simple discount patient access scheme (PAS).

3 REVIEW OF COMPANY'S CONSULTATION RESPONSE

The company arranged their response into eleven issues which we review in turn below.

3.1 Updated Patient Access Scheme (PAS)

The company has updated its simple discount patient access scheme for setmelanotide to [redacted]. This is implemented correctly in the companys updated model, and all results provided in the company's response. All of the results provided by the EAG in section 5 , use the updated PAS price.

3.2 Proportion of moderate and severe patients at baseline

The company have updated their base-case to include a proportion of patients with moderate hyperphagia at baseline to reflect the marketing authorisation which does not restrict use of setmelanotide based on severity of hyperphagia. Whilst the company accepts that the split of BBS patients with obesity in clinical practice is approximately 60% severe and 40% moderate hyperphagia, it argues that setmelanotide would be given preferentially to severe patients based on need and likely treatment response. For this reason the company suggests the split would be closer to 75% and 25% for severe and moderate hyperphagia respectively in clinical practise, and this is what is used in the companys updated base-case.

The EAG believes it is likely that all patients that meet the marketing authorisation would be considered for treatment with setmelanotide, regardless of hyperphagia severity, and so

prefer to use 60% and 40% for severe and moderate hyperphagia respectively in the EAGs updated base-case.

3.3 Diagnosis of severe hyperphagia

The company argue that BBS patients with moderate and severe hyperphagia can be distinguished in practise by multi-disciplinary teams in specialist centres. They also point out the differences between the definitions in the vignettes between moderate and severe hyperphagia (Appendix A of company response to the draft guidance consultation), which are largely based on increased frequency of behaviours. However, they include both severe and moderate hyperphagia patients in their updated base-case (Section 3.2).

The company do not present new information for diagnosis of severe hyperphagia and the EAG comments are unchanged from previous documents. In clinical practice, hyperphagia severity will be assessed prospectively, in advance of treatment initiation. In clarification response A1, the company noted the challenges of prospective assessment of hyperphagia, particularly in relation to the assessment of hunger and overeating symptoms. The company also noted that the participants of their main trial (RM-493-023) could not have their hyperphagia severity assessed at baseline entry to the study, as there is no validated measure of hyperphagia severity. We refer to Key Issue 1 of the EAG report and to the EAG post-technical engagement response document where this issue is discussed in more detail.

3.4 Modelling baseline severity and variable treatment effect

We thank the company for explaining how their model could be used to model both a proportion in moderate hyperphagia at baseline and a variable treatment effect on hyperphagia in responders. The EAG had been changing the inputs in the “Detailed Inputs” sheet, but that was not linked up to the model calculations, and so wasn’t being implemented.

The company have provided (deterministic) results for different combinations of:

- baseline hyperphagia distributions: (i) 100% severe; (ii) 75% severe, 25% moderate; and (iii) 60% severe, 40% moderate.
- treatment effects on hyperphagia for a given starting hyperphagia state: (a) All severe and moderate move to no hyperphagia (utility multiplier of 1); (b) All severe move to mild and all moderate move to no hyperphagia; (c) All severe and moderate move to mild. Note there some typo’s in the description of these options in the company’s consultation response, but they are described correctly in the file providing the cost-effectiveness results.

Note that the company’s scenarios include patients moving to “no hyperphagia” which was not previously included in the model. They achieved this by changing the utility multipliers in the calculations sheet of their model to set them to 1 for “no hyperphagia”.

Case (cii) represents the company's updated base-case, but the results in Table 2 differ slightly from those in Table 1 due to Table 2 reporting results from a deterministic model and Table 1 reporting the probabilistic results.

As noted in section 3.2, the EAG prefers a baseline population of 60% severe, 40% moderate (case (iii)). For the treatment effect, the EAG is happy with the companys assumption that 100% of moderate patients move to mild hyperphagia, however the EAG still believes that a proportion of severe patients would move to moderate, and this is also in line with the committee's preference as described in the draft guidance consultation. The EAG therefore retains the assumption that [redacted] of severe patients would move to mild and [redacted] would move to moderate hyperphagia (as described in the EAG report, section 4.2.6.3).

3.5 Paediatric or mixed population at initiation

The company argues that it is appropriate to consider initiation of setmelanotide in paediatrics, rather than in a mixed population of adults and children. This is based on a study (Pomeroy 2021) that shows obesity rates exceeds 90% of BBS patients by 5-years, and the likelihood of increased screening and genetic testing in the future. The company does however provide a scenario using the mixed population (60% paediatric).

As noted in the EAG report, the EAG heard that although more BBS patients are being diagnosed in childhood, it would be a long time before all patients were diagnosed as children, and so it seems appropriate to include adults in a scenario. The EAG also note that the committee's preference was for the mixed population, and so the EAG provide results for both the paediatric and mixed populations.

3.6 Treatment effect on BMI-Z class-shifts

The company has updated its base-case to incorporate a treatment effect on BMI-Z in paediatrics with a [redacted] average class change, to reflect the clinical trial evidence that the class change is between [redacted] and [redacted]. This is achieved in the model by forming a weighted average of the results for a [redacted] change and a [redacted] change. The company also provides a scenario with a [redacted] average class change which is derived from an analysis of the clinical trial data that adjusts for a placebo effect.

The EAG is considers the weighted average approach to be appropriate given the model structure, but prefers to use the placebo adjusted average class change of [redacted] to be a less biased estimate of treatment efficacy. The placebo-adjusted average class change is used in the EAG's updated base-case.

3.7 Discontinuation

The EAG had assumed a discontinuation rate of 2% based on clinical trial data that the company had provided giving discontinuations and reasons for discontinuation from RM-493-023. However, in the company's consultation response, they explain that this was based

on [redacted] who in fact had not responded and were modelled as such in the model. They therefore prefer a 1% discontinuation rate, as in their base-case.

The EAG acknowledges that non-responders would not continue with setmelanotide, and so would not count towards the long-term discontinuation rate. The EAG still notes the high level of uncertainty around the long-term discontinuation rate for setmelanotide, but has changed its base-case to use a 1% discontinuation rate, but provides a scenario with the EAG updated base-case and a 2% discontinuation rate. The company has also run a scenario with a 2% discontinuation rate applied to its updated base-case. This shows a small reduction in the ICER compared to a 1% discontinuation rate, but a large reduction in the undiscounted Quality Adjusted Life Years (QALYs) from [redacted] (1% discontinuation rate) to [redacted] (2% discontinuation rate) for the company's base-case. The choice of discontinuation rate therefore has consequences for the appropriate QALY weighting.

3.8 Implementation of carer-disutility

The company has confirmed that their model only includes the carer-disutility for patients who are not responding to treatment (ie on BSC), which is in line with the committee's preference. The EAG apologises for not picking this up, partly because it was not described in the companys submission or documented in the model. The EAG is happy that the company models carer-disutility for non-responders appropriately.

3.9 Number of care-givers per adult BBS patient

The company has updated the base-case assumptions to [redacted] caregivers for adults (based on clinical expert opinion) instead of [redacted] which was used previously (based on data from the BBS UK Survey).

The EAG is not entirely clear of the rationale for this change, and prefers the estimate based on data from the BBS UK Survey, although notes that the EAG has not been sent this data to review. The EAG retains [redacted] caregivers for adults in its base-case.

3.10 Clinical benefits of setmelanotide

The company provide further evidence to support the clinical benefits of setmelanotide:

1. Abstracts from conferences (Haqq et al. 2023 TOS and ESPE) on the association between setmelanotide treatment response and reductions in metabolic syndrome severity scores in patients with BBS from RM-493-023. Metabolic syndrome severity score is associated with reduced risk of metabolic syndrome, cardio-vascular disease and type 2 diabetes.

   The EAG note that the small numbers of patients in RM-493-023 mean that there is still substantial uncertainty, although these results show a trend in the direction indicated by the company. The EAG does, however, consider that setmelanotide is likely to be clinically effective, and that the model appropriately includes benefits of setmelanotide in reduction of cardio-vascular events, and type 2 diabetes.

2. EOObesity model data. The company has provided a technical report (EOObesity) of some modelling work which predicts the impact of early-onset obesity on co-morbidity and mortality over time (Appendix B of company comments on the draft guidance consultation). They found that this modelling work predicted a bigger impact of obesity on co-morbidity and mortality then they had used in their model for setmelanotide. Incorporating these estimates in their model for setmelanotide, led to improved estimates of QALY gains in a scenario analysis provided by the company.

   The EAG are supportive of using estimates of the impact of obesity on comorbidities based on an appropriate population (early-onset obesity), rather than utilising data from adults with obesity, although it is not clear to the EAG how much of the model inputs were derived from data on children. The technical report from the EOObesity study describes a model that is built from a range of data-sources and modelling assumptions. The EAG did not have the resources to review this work in detail, but notes that many of the studies included in the companys model are also included in EOObesity, however EOObesity includes more studies from a broad range of countries, rather than being UK specific. There may therefore be issues with generalisability to a UK population. EOObesity models the impact of age and duration of obesity on co-morbidities, however the detail on how exactly this is achieved isn't given in the report. EOObesity includes the impact of obesity on cancer, which is not included in the companys model, including cancer.

3. Clinical expert opinion. The company highlights that clinical experts indicated that it was unlikely that patients would gain weight on setmelanotide, unless due to puberty or con-concomitant medicines. Clinical experts also highlighted the benefits of a reduction in hyperphagia, even in the absence of weight loss.

3.11 Conservative nature of the model

The Company outline seven areas where they feel their model is conservative:

1. Treatment effect after discontinuation. The company point out that patients who discontinue setmelanotide immediately return to their state at baseline, when in fact they will experience a tapering of the benefit in practise.

   Whilst the EAG agree that this is true, the company's model also assumes that the benefits of setmelanotide continue into the long-term without waning, which is likely to over-estimate the benefits of setmelanotide, and may outweigh the effects of not including a tapering effect in those who discontinue.

2. Hyperphagia treatment effect. The company's model assumes that all patients move to mild hyperphagia, but in practice some may move to "no hyperphagia" and receive increased utility benefits.

The EAG agrees that there may be some patients whose hyperphagia is completely eliminated, but there will also be patients who move to moderate rather than mild hyperphagia. It can be seen from the hunger scores collected in RM-493-023 that there is variability across patients. It is therefore not clear to the EAG that there will be a net under-estimation of utility benefits.

3. Hyperphagia at baseline. The company believes that there is likely to be a higher response rate in patients with severe hyperphagia compared with those with moderate hyperphagia, and so there would be more severe patients responding to setmelanotide, which would increase the utility benefits.

   The EAG has not seen any data on response rates by severity of hyperphagia, but it is possible that response may be more likely in more severe patients. Even so, it is not necessarily that case that the utility benefits due to reduced hyperphagia and BMI-Z / BMI would be higher in those with initial severe hyperphagia, without seeing data to support this.

4. Upper limit of BMI-Z class (>4). The company note that in RM-493-023 there were patients with extremely high (BMI / BMI-Z of 5.5 or 7), but their model does not capture the comorbidity and mortality benefits for patients with very high BMI / BMI-Z.

   The EAG agrees that the BMI-Z / BMI categories used are likely to underestimate the benefits for patients with extremely high BMI / BMI-Z.

5. Rate of obesity-related comorbidities in early-onset obesity. The EOObesity data model predicts a lower life expectancy for untreated patients, and when this is included in the companys model predicts higher QALY gains.

   See response in section 3.10 point 2 for the EAGs comments on the EOObesity study. The model inputs and modelling used in that study would need to be critiqued from a UK BBS population perspective to assess the relevance for decision-making.

6. Limited list of co-morbidities associated with early-onset obesity. The company note that they did not include all co-morbidities associated with early-onset obesity, such as skin lesions, which have a detrimental effect on quality of life (Hasse et al., 2023). The health related quality of life (HRQoL) benefits are therefore likely to be under-estimates.

   The EAG agrees that not all co-morbidities associated with obesity have been included in the model, and this may under-estimate HRQoL benefits.

7. Ethnic minority considerations. The company note that:
   - people from Black, Asian and minority ethnic family backgrounds “have an increased cardiometabolic health risk at lower BMI thresholds” (NICE CG189)
   - BBS disproportionately affects people from ethnic background where consanguineous marriage is more commonly practiced

However, the data on which their model is built is based largely on patients from Caucasian backgrounds, which may not represent these ethnic groups.

The EAG agree that the extrapolation of evidence from Caucasian patients may not fully reflect the costs and benefits of setmelanotide in these ethnic groups. The EAG has previously noted that the patients included in RM-493-023 may not be representative of the UK BBS population, with some ethnic groups (eg South Asians) under-represented.

4 COMPANY's UPDATED ANALYSES

The company has provided an updated base-case and scenario analyses in the file "[ID3947] revised cost-effectiveness results from company [CIC].docx". The company's updated base-case assumes:

- A 100% paediatric initiated population
- A baseline population of 75% severe hyperphagia and 25% moderate hyperphagia
- Weighted average of [redacted] & [redacted] BMI-Z class shift [average class shift of [redacted]
- 1% discontinuation rate
- EAG-corrected mapping of BMI-Z PedsQL scores to EQ-5D
- Ongoing weight management monitoring costs
- [redacted] adult caregivers

Note that the "EAG-corrected mapping of BMI-Z PedsQL scores to EQ-5D" is the scenario in response to Key Issue #9 at technical engagement with the EAG correction. This was used in the EAG base-case following technical engagement, however we note from the draft guidance that this was not the committee's preference. The committee instead preferred the scenario in response to Key Issue #10 at technical engagement with the EAG correction.

The company ran the following scenarios:

- Scenario 1: Mixed Population [60% paediatric]
- Scenario 2: [redacted] BMI-Z average class shift, to account for placebo effect
- 2% discontinuation rate
- Mapping correction for lit-based EQ-5D
- EOObesity-Model mortality and comorbidities
- Different combinations of: baseline hyperphagia distributions and treatment effects on hyperphagia (see section 3.4)

The EAG is unclear exactly what the "mapping correction for lit-based EQ-5D" scenario represents, as it is not mentioned in the company comments on the draft guidance consultation, but assumes that this is the approach using Riazi et al (2010) utility values and extrapolation, using a correction to the mapping method.

5 EAGs UPDATED ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the EAG

All of the EAGs scenario analyses were applied to the company's updated base-case model received by the EAG on 25/08/23 following comments on the draft guidance.

The EAG conducted the following scenarios:

- Scenario 1: Initial severity of hyperphagia where 60% of patients have severe hyperphagia, and 40% have moderate hyperphagia.
- Scenario 2: Treatment effect on hyperphagia with [redacted] of patients moving to mild, and [redacted] to moderate.
- Scenario 3: Treatment effect on BMI-Z where paediatric patients who respond to treatment achieve a BMI-Z / BMI average class reduction of [redacted].
- Scenario 4: [redacted] caregivers for adults based on BBS UK survey
- Scenario 5: Baseline utilities from Riazi et al. (2010) as described in Key issue 10 of the companys technical engagement response, with the EAG's corrected BBS utility multiplier of [redacted] (see EAG response to the companys technical engagement comments).

The results from the EAGs scenario analyses are shown for the paediatric population in Table 1 and for the mixed (60% paediatric, 40% adult) population in Table 2**Error! Reference source not found.**. All EAG results shown are from a probabilistic analysis.

TABLE 1 EAGS ADDITIONAL SCENARIO ANALYSES APPLIED TO THE COMPANY'S UPDATED BASE CASE MODEL PAEDIATRIC POPULATION (PROBABILISTIC RESULTS DISPLAYED)

No.	Scenario	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
0	Company's updated base case (probabilistic)	[redacted]	[redacted]	[redacted]	£197,588
1	Initial severity of hyperphagia split (60% severe)	[redacted]	[redacted]	[redacted]	£210,411
2	Treatment effect on hyperphagia ([redacted] of severe move to mild, [redacted] to moderate)	[redacted]	[redacted]	[redacted]	£215,642
3	Treatment effect on BMI-Z average class reduction of [redacted]	[redacted]	[redacted]	[redacted]	£201,510
4	Number of carers for adults = [redacted]	[redacted]	[redacted]	[redacted]	£209,460
5	Baseline utilities from literature with BBS utility multiplier = [redacted]	[redacted]	[redacted]	[redacted]	£188,813
All	1 + 2 + 3 + 4 + 5	[redacted]	[redacted]	[redacted]	£236,081

TABLE 2 EAGS ADDITIONAL SCENARIO ANALYSES APPLIED TO THE COMPANY'S UPDATED BASE CASE MODEL MIXED 60% PAEDIATRIC 40% ADULT POPULATION (PROBABILISTIC RESULTS DISPLAYED)

No.	Scenario	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
0	Company's updated base case (probabilistic)	[redacted]	[redacted]	[redacted]	£202,327
1	Initial severity of hyperphagia split (60% severe)	[redacted]	[redacted]	[redacted]	£215,676

2	Treatment effect on hyperphagia (of severe move to mild, to moderate)	[redacted]	[redacted]	[redacted]	£220,904
3	Treatment effect on BMI-Z average class reduction of	[redacted]	[redacted]	[redacted]	£205,498
4	Number of carers for adults =	[redacted]	[redacted]	[redacted]	£217,322
5	Baseline utilities from literature with BBS utility multiplier =	[redacted]	[redacted]	[redacted]	£193,124
All	1 + 2 + 3 + 4 + 5	[redacted]	[redacted]	[redacted]	£243,672

5.2 EAG updated base-case

The EAG's preferred assumptions are:

1. Initial severity of hyperphagia where 60% of patients have severe hyperphagia, and 40% have moderate hyperphagia
2. Treatment effect on hyperphagia with of severe moving to mild and to moderate, and of moderate moving to mild
3. Treatment effect on BMI-Z an average class reduction of for the paediatric BBS population
4. Number of caregivers for adults set to
5. Baseline utilities from Riazi et al. as described in Key issue 10 of the companys technical engagement response, with the EAG's corrected BBS utility multiplier of (see EAG response to the companys technical engagement comments).

The results for the for the EAGs preferred assumptions are shown for the paediatric population in Table 3, and for the mixed (60% paediatric, 40% adult) population in Table 4.

TABLE 3 COST-EFFECTIVENESS RESULTS FOR THE EAGS UPDATED BASE-CASE: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,588
+ Initial severity of hyperphagia 60% severe and 40% moderate (assumption 1)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£210,411
+ treatment effect on hyperphagia: [redacted] severe to mild [redacted] severe to moderate; [redacted] moderate to mild (assumptions 1 + 2)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£227,832
+ treatment effect on BMI-Z average class reduction of [redacted] (assumptions 1 + 2 + 3)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,608
+ number caregivers for adults [redacted] (assumptions 1 + 2 + 3 + 4)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£247,401
+ Baseline utilities from literature with BBS utility multiplier = [redacted] (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£236,081

TABLE 4 COST-EFFECTIVENESS RESULTS FOR THE EAGS UPDATED BASE-CASE: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£202,327
+ Initial severity of hyperphagia 60% severe and 40% moderate (assumption 1)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£215,676
+ treatment effect on hyperphagia: [redacted] severe to mild [redacted] severe to moderate; [redacted] moderate to mild (assumptions 1 + 2)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£233,416
+ treatment effect on BMI-Z average class reduction of [redacted] (assumptions 1 + 2 + 3)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£234,632
+ number caregivers for adults [redacted] (assumptions 1 + 2 + 3 + 4)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£256,149
+ Baseline utilities from literature with BBS utility multiplier = [redacted] (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£243,672

5.3 Additional Scenario (EAG Updated base-case with discontinuation rate 2%)

The EAG notes in section 3.7 a high level of uncertainty around the long-term discontinuation rate for setmelanotide. Results from an additional scenario with a 2% discontinuation rate applied to the EAG's updated base case are shown for the paediatric population in Table 5 and the mixed (60% paediatric, 40% adult) population in Table 6.

TABLE 5 COST-EFFECTIVENESS RESULTS FOR AN ADDITIONAL SCENARIO APPLIED TO THE EAGS UPDATED BASE-CASE: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG's updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£236,081
2% treatment discontinuation applied to EAG's updated base case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£233,531

TABLE 6 COST-EFFECTIVENESS RESULTS FOR AN ADDITIONAL SCENARIO APPLIED TO THE EAGS UPDATED BASE-CASE: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG's updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£243,672
2% treatment discontinuation applied to EAG's updated base case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,925

6 QALY Weighting

In the companys updated base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the EAG preferred base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). Whilst all these figures are uncertain and based on strong assumptions, the EAG considers that it is plausible that a QALY weighting may apply in the paediatric population. The EAGs base-case estimate would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

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EVIDENCE FOR DECISION MAKERS

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG Additional Analysis Requested by Committee following ECM2

Produced by: Bristol Technology Assessment Group, University of Bristol

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[redacted]

[redacted]

ABBREVIATIONS

Abbreviation	Definition
EAG	Evidence Assessment Group
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

1 INTRODUCTION

The HST committee requested the EAG to provide results for the EAG base-case presented at ECM2 with the number of adult carers set to 1.

2 MODEL ASSUMPTIONS

The EAG base-case model is described in section 5.2 of the EAG response to consultation comments for ECM2, summarised below with the change in adult carers:

The EAG's preferred assumptions are:

1. Initial severity of hyperphagia where 60% of patients have severe hyperphagia, and 40% have moderate hyperphagia
2. Treatment effect on hyperphagia with [redacted] of severe moving to mild and [redacted] to moderate, and [redacted] of moderate moving to mild
3. Treatment effect on BMI-Z an average class reduction of [redacted] for the paediatric BBS population
4. Number of caregivers for adults set to 1.0
5. Baseline utilities from Riazi et al. as described in Key issue 10 of the companys technical engagement response, with the EAG's corrected BBS utility multiplier of [redacted] (see EAG response to the companys technical engagement comments).

The results for this model are shown for the paediatric population in Table 1, and for the mixed (60% paediatric, 40% adult) population in Table 2.

**TABLE 1 COST-EFFECTIVENESS RESULTS FOR THE EAG BASE CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,588
EAG base-case at ECM2							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£236,081
EAG base-case at ECM with 1 carer for adult patients							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£231,902

TABLE 2 COST-EFFECTIVENESS RESULTS FOR THE EAG BASE-CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£202,327
EAG base-case at ECM2							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£243,672
EAG base-case at ECM2 with 1 adult carer							

BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,259

2.1 Additional Scenario (EAG Updated base-case with discontinuation rate 2%)

The EAG notes a high level of uncertainty around the long-term discontinuation rate for setmelanotide. Results from an additional scenario with a 2% discontinuation rate applied to the EAG's base case at ECM2 with 1 carer per adult patient are shown for the paediatric population in Table 3 and the mixed (60% paediatric, 40% adult) population in Table 4.

TABLE 3 COST-EFFECTIVENESS RESULTS FOR A SCENARIO ANALYSIS WITH 2% DISCONTINUATION RATE APPLIED TO THE EAG BASE-CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£231,902
2% treatment discontinuation applied to EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£228,925

TABLE 4 COST-EFFECTIVENESS RESULTS FOR A SCENARIO ANALYSIS WITH 2% DISCONTINUATION APPLIED TO THE EAG BASE-CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,259

2% treatment discontinuation applied to EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£235,383

3 QALY Weighting

In the companys updated base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the EAG base-case at ECM2 with 1 carer per adult patient, the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). The EAG base-case at ECM2 with 1 carer per adult patient would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

Rationale supporting the identified inaccuracies and misinterpretations in NICE decision-making

1. Error in the estimate of the proportion of patients with a ≥[redacted]-level shift in BMI-Z

Approach taken by the EAG: the EAG assumes that patients who achieved a BMI-Z shift of ≥[redacted] levels move from severe hyperphagia to mild hyperphagia. To determine the proportion of patients who achieve this [redacted] level or greater shift in BMI-Z, they used the original BMI-Z shift data with broader BMI-Z classes (table 35 in CS), resulting in an estimate of [redacted] of patients achieving a [redacted]-level shift.

Errors associated with the EAG approach: within the DG, the committee indicated that the potential impact of the placebo effect should be explored. In response to this, we submitted an updated table including placebo corrected data of the BMI-Z shifts based on the more granular BMI-Z classes previously accepted by the EAG (Appendix C). This updated table should be used to estimate the proportion of patients who achieved a BMI-Z shift of ≥[redacted] levels and move from severe to mild hyperphagia, rather than the EAG's approach. Particularly, since as part of its conclusions, the committee preferred to use the placebo corrected data for the weighted average of mean class reduction.

Impact of the EAG's error:

Based on the BMI-Z shift data table shared with our response to the DG (placebo-corrected):

- [redacted] out of [redacted] responder patients experienced a BMI-Z shift of ≥[redacted] levels (including [redacted] achieving [redacted] levels and [redacted] achieving [redacted] levels), i.e., [redacted] of patients with severe hyperphagia should be considered to move to mild hyperphagia
- [redacted] out of [redacted] responder patients experience a BMI-Z shift of [redacted] levels, i.e. [redacted] of patients with severe hyperphagia should be considered to move to moderate hyperphagia (as we explain in the section below)

Contrary to the EAG's claim, using these numbers **has a significant impact on both the ICER and the undiscounted QALYs** and thus on the expected outcome of the submission. If the NICE team or EAG would like further information on this, we are happy to provide an Excel spreadsheet providing details on these calculations.

2. Misinterpretation in the assumption that responder patients with a BMI-Z shift of 0 levels do not experience an effect on hyperphagia

Approach taken by the EAG: the EAG has assumed that if a patient does not move BMI-Z classes, the patient will remain with in severe hyperphagia state.

Errors associated with the EAG approach: the EAGs approach is flawed and does not take into account the model structure and evidence submitted:

- The model is a responder-based model (i.e., the BMI-Z shift data relates only to patients who are qualified as responders, and so have shown a clinically meaningful reduction in weight / BMI / BMI-z)
- Change in eating habits and consequent change in weight / BMI / BMI-z can only result from an improvement in hyperphagia
- Any patient that did not experience an effect on hyperphagia would not achieve a clinically meaningful reduction in weight / BMI / BMI-z and so would be classed as non-responders and would not be included in the BMI-Z shift data

Based on this, it is not logical or appropriate to assume that a **responder** would remain at the same hyperphagia level at 52 weeks and at baseline.

Impact of the EAG's error:
[redacted] out of [redacted] responder patients, i.e. [redacted] of patients with severe hyperphagia should be considered to move from severe to moderate hyperphagia.

Contrary to the EAG's claim, using these numbers **has a significant impact on both the ICER and the undiscounted QALYs** and thus on the expected outcome of the submission.

To avoid inaccuracy, it is appropriate for the base-case to be updated to show that responder patients experiencing 0-class shift **move from Severe to Moderate hyperphagia**.

3. <u>Misinterpretation that 60% of BBS patients have severe hyperphagia and 40% have moderate hyperphagia, reflects the patient mix that would be treated with setmelanotide</u>

We are not disputing the clinical expert opinion that within the whole BBS population (both adults and children), 60% of patients have severe hyperphagia and 40% have moderate hyperphagia. This number was stated in the Clarification response, and it was confirmed by the clinical expert during the Committee meeting. This has been **misunderstood** as being the target population for the economic model, which is not the case. The relevant population is: **BBS patients with obesity (as per labelled indication) who would be treated with setmelanotide in the 4 specialized BBS centres** – i.e., not all BBS patients present with obesity.

In our initial model we considered that the BBS patients with obesity and severe hyperphagia would be prioritized for treatment with setmelanotide. Listening to physicians and the patient organisation at the first committee meeting, we revised that assumption to 75% of patients treated having severe hyperphagia and 25% of patients treated having moderate hyperphagia at baseline to reflect the treatment eligible population.

We believe the question that needed to be posed to experts during the committee meeting to establish the validity of this estimate is: of the BBS patients with obesity, what would be the proportion of patients with severe and moderate hyperphagia prioritized for treatment with setmelanotide? Based on data from publications we show below that our estimates are realistic, but it may be beneficial to consult the clinical experts on their view to this question.

To support our rationale, we note that Pomeroy 2021, estimates that approximately 70% of children with BBS are obese. Considering that all patients with severe hyperphagia would be obese, it stands to reason that the proportion of patients with moderate hyperphagia in the treated population would be <40%. Based on the estimate in Pomeroy 2021:

- 60% of BBS population has severe hyperphagia and thus is obese
- 10% of BBS population is obese and has moderate hyperphagia
- Combining the above, the proportions in the treated population would be 86% of patients (60% out of 70%) with severe hyperphagia and 14% of patients (10% out of 70%) with moderate hyperphagia

This shows that our model uses a conservative and reasonable assumption for the proportion of patients with severe and moderate hyperphagia in the target population, i.e. BBS patients with obesity.

EAG Response to: Rationale supporting the identified inaccuracies and misinterpretations in NICE decision-making

1. *Error in the estimate of the proportion of patients with a ≥[redacted]-level shift in BMI-Z*

Approach taken by the EAG: *the EAG assumes that patients who achieved a BMI-Z shift of ≥[redacted] levels move from severe hyperphagia to mild hyperphagia. To determine the proportion of patients who achieve this [redacted] level or greater shift in BMI-Z, they used the original BMI-Z shift data with broader BMI-Z classes (table 35 in CS), resulting in an estimate of [redacted] of patients achieving a [redacted]-level shift.*

Errors associated with the EAG approach: *within the DG, the committee indicated that the potential impact of the placebo effect should be explored. In response to this, we submitted an updated table including placebo corrected data of the BMI-Z shifts based on the more granular BMI-Z classes previously accepted by the EAG (Appendix C). This updated table should be used to estimate the proportion of patients who achieved a BMI-Z shift of ≥[redacted] levels and move from severe to mild hyperphagia, rather than the EAG's approach. Particularly, since as part of its conclusions, the committee preferred to use the placebo corrected data for the weighted average of mean class reduction.*

EAG Response: The EAG agrees that placebo-adjusted responses are preferred. The EAG also agrees that finer class definitions may be more appropriate, although note that the classes need to match those used in the model. As explained in the ECM2 committee meeting the EAG did not change the proportion of patients who move from severe to mild hyperphagia because using the alternative approaches give very similar results. The EAG sees two alternative ways to approach this, as explained at ECM2.

i) If we use the average [redacted] class-shift after adjusting for placebo response, this is equivalent to [redacted] with a [redacted]-class shift and [redacted] with a [redacted]-class shift. This gives a very similar proportion to the 58% assumed in the EAG base-case, and so we would expect the results to be similar.

ii) If we use the proportion of patients with a [redacted]-class shift from the BMI-Z shifts based on the more granular BMI-Z classes provided by the company in Appendix C of their comments on the draft guidance consultation, then [redacted] of patients achieve a [redacted]-class shift (or more) and [redacted] achieve a [redacted] class-shift. If we assume those with a [redacted]-class shift move to mild hyperphagia, and those with a [redacted] class-shift remain in severe hyperphagia, then the average utility multiplier is [redacted] = [redacted] + [redacted] This is very similar to the average utility multiplier from the EAG base-case of [redacted] ([redacted] + [redacted]*[redacted]), and so would give very similar results.

The EAG acknowledges that (i) or (ii) are preferred approaches, but since the results are very similar does not feel that the approach taken is an "error".

Impact of the EAG's error:

Based on the BMI-Z shift data table shared with our response to the DG (placebo-corrected):

- [redacted] out of [redacted] responder patients experienced a BMI-Z shift of [redacted] levels (including [redacted] achieving [redacted] levels and [redacted] achieving [redacted] levels), i.e., [redacted]% of patients with severe hyperphagia should be considered to move to mild hyperphagia

- [redacted] out of [redacted] responder patients experience a BMI-Z shift of [redacted] levels, i.e. [redacted]% of patients with severe hyperphagia should be considered to move to moderate hyperphagia (as we explain in the section below)

Contrary to the EAG's claim, using these numbers **has a significant impact on both the ICER and the undiscounted QALYs** and thus on the expected outcome of the submission. If the NICE team or EAG would like further information on this, we are happy to provide an Excel spreadsheet providing details on these calculations.

EAG Response: As described in (ii) above, the EAG has assumed that the patients that experience a BMI-Z shift of 0 levels would not change their hyperphagia state, and as shown above this gives an average utility multiplier that is very similar to the EAGs base-case, and so would not have an impact on the ICER or undiscounted QALYs. This assumption is also consistent with the average BMI-Z class shift of [redacted] (approach (i) above), which also gives a very similar utility multiplier as the EAG base-case. We agree however, that if patients with a 0 class BMI-Z shift are assumed to move to moderate hyperphagia, then this would have a significant impact on both the ICER and the undiscounted QALYs.

2. *Misinterpretation in the assumption that responder patients with a BMI-Z shift of 0 levels do not experience an effect on hyperphagia*

Approach taken by the EAG: *the EAG has assumed that if a patient does not move BMI-Z classes, the patient will remain with in severe hyperphagia state.*

Errors associated with the EAG approach: *the EAGs approach is flawed and does not take into account the model structure and evidence submitted:*

- *The model is a responder-based model (i.e., the BMI-Z shift data relates only to patients who are qualified as responders, and so have shown a clinically meaningful reduction in weight / BMI / BMI-z)*
- *Change in eating habits and consequent change in weight / BMI / BMI-z can only result from an improvement in hyperphagia*
- *Any patient that did not experience an effect on hyperphagia would not achieve a clinically meaningful reduction in weight / BMI / BMI-z and so would be classed as non-responders and would not be included in the BMI-Z shift data*

Based on this, it is not logical or appropriate to assume that a ***responder*** *would remain at the same hyperphagia level at 52 weeks and at baseline.*

EAG Response: The EAG's model assumes that [redacted] of patients move to mild hyperphagia and [redacted] to moderate, and so does not assume that any patients remain in severe hyperphagia. If we use alternative (i) above then these proportions would change very slightly, but still no patients assumed to remain in severe hyperphagia. If we use alternative (ii) above then the patients who did not move BMI-Z class are assumed to remain in severe hyperphagia because they did not experience a class-change in BMI-Z. The company argues that only responders would receive setmelanotide, and so would achieve a class-change in BMI-Z. However, the data they provided in Appendix C of their comments on the draft guidance consultation were on "responders" from their study, yet [redacted] had a 0 class-shift in BMI-Z.

Impact of the EAG's error:
[redacted] out of [redacted] responder patients, i.e. [redacted]% of patients with severe hyperphagia should be considered to move from severe to moderate hyperphagia.

Contrary to the EAG's claim, using these numbers ***has a significant impact on both the ICER and the undiscounted QALYs*** *and thus on the expected outcome of the submission.*

To avoid inaccuracy, it is appropriate for the base-case to be updated to show that responder patients experiencing 0-class shift ***move from Severe to Moderate hyperphagia****.*

EAG Response: As noted above these [redacted] of patients had a 0 class change in BMI-Z with the more granular class categories, which suggests that there was a minimal improvement in hyperphagia for these patients. See our responses above on this point. The significant impact on ICER and undiscounted QALYs is only the case if the patients who were responders in the trial but had a 0 class change in BMI-Z using the granular categorisation are assumed to move to moderate hyperphagia.

3. *Misinterpretation that 60% of BBS patients have severe hyperphagia and 40% have moderate hyperphagia, reflects the patient mix t+-hat would be treated with setmelanotide*

We are not disputing the clinical expert opinion that within the whole BBS population (both adults and children), 60% of patients have severe hyperphagia and 40% have moderate hyperphagia. This number was stated in the Clarification response, and it was confirmed by the clinical expert during the Committee meeting. This has been ***misunderstood*** *as being the target population for the economic model, which is not the case. The relevant population is:* ***BBS patients with obesity (as per labelled indication) who would be treated with setmelanotide in the 4 specialized BBS centres*** *– i.e., not all BBS patients present with obesity.*

In our initial model we considered that the BBS patients with obesity and severe hyperphagia would be prioritized for treatment with setmelanotide. Listening to physicians and the patient organisation at the first committee meeting, we revised that assumption to 75% of patients treated having severe hyperphagia and 25% of patients treated having moderate hyperphagia at baseline to reflect the treatment eligible population.

We believe the question that needed to be posed to experts during the committee meeting to establish the validity of this estimate is: of the BBS patients with obesity, what would be the proportion of patients with severe and moderate hyperphagia prioritized for treatment with setmelanotide? Based on data from publications we show below that our estimates are realistic, but it may be beneficial to consult the clinical experts on their view to this question.

To support our rationale, we note that Pomeroy 2021, estimates that approximately 70% of children with BBS are obese. Considering that all patients with severe hyperphagia would be obese, it stands to reason that the proportion of patients with moderate hyperphagia in the treated population would be <40%. Based on the estimate in Pomeroy 2021:

- *60% of BBS population has severe hyperphagia and thus is obese*
- *10% of BBS population is obese and has moderate hyperphagia*

- *Combining the above, the proportions in the treated population would be 86% of patients (60% out of 70%) with severe hyperphagia and 14% of patients (10% out of 70%) with moderate hyperphagia*

This shows that our model uses a conservative and reasonable assumption for the proportion of patients with severe and moderate hyperphagia in the target population, i.e. BBS patients with obesity.

EAG Response: We agree that the proportion of severe hyperphagia at baseline should be with respect to the BBS population with obesity. The companys argument above assumes that the 60:40 split between severe and moderate hyperphagia is in the full BBS population including those who are not obese. The EAG had understood this to be for the obese BBS population who would be considered for treatment with setmelanotide. This is implied in the companys comments on the draft guidance consultation Comment#2: "*The draft guidance refers to the split of severe and moderate hyperphagia in BBS patients with obesity in clinical practice to be 60% severe and 40% moderate. Whilst Rhythm accepts that this is the split of patients in clinical practice, … "* and also in their original submission, section B.3.15: "*It is estimated that approximately 60% of obese BBS patients have severe hyperphagia (KOL opinion)".*

Dear Celia
Thank you for your email. I must admit I struggled with this question as there is not enough data to support an evidence based answer. I have done my best to answer the question below and hope my answer is helpful to the NICE team. If anyone from the team would like to discuss it with me further I am very happy to speak.

As I understand it, the question is asking for the average expected change in hyperphagia in relation to magnitude of change in BMI-Z score.

In addition to what is published and freely available I can add my own experience and what I have heard from the other investigators of the phase III trial in conversations when we were putting together the paper. From this it was clear that the patients who responded to treatment appeared to have a significant effect on their hunger and hyperphagia consistent with what I would interpret as a move from severe or moderate hyperphagia to mild or no hyperphagia. This translated into an improvement in quality of life.

There were 32 patients with BBS in the phase III trial. I do not feel that I can provide an evidence based average response for different subgroups on the information we currently have available. I do hope this makes sense. If I have misunderstood something, or if I can provide clarification or more help I am very happy to do so.

bw
Elizabeth

Dr Elizabeth Forsythe
MBBS BMedSci PhD MRCPCH
Genomics and Genetic Medicine Programme
UCL Great Ormond Street Institute of Child Health
London

Dear Celia,

Thank you for your email. My thoughts below.

1. It is impossible to provide percentages when the n number of patients per group is very small and well below 100. And this is for the world-wide published experience. The subgroups would be even smaller.
2. Will make an attempt to describe my expectations and my understanding of the literature, considering the limitations.
3. The vast majority of patients will have severe hyperphagia as it will be these patients who will present more frequently to any healthcare professionals, more likely to be referred to specialist services if already known to healthcare professionals and more likely to be prioritised for treatment if already in services.
4. Individuals with severe hyperphagia what a reduction of BMI-Z score >2: would expect most of them to achieve mild, with a proportion to achieve no hyperhagia as the group has had a great response to the treatment in terms of weight loss maintenance.
5. Individuals with severe hyperphagia what a reduction of BMI-Z score <1: Would expect most people to achieve moderate hyperphagia with a small proportion achieving mild. Again this group had a response to treatment so there will be an improvement.
6. Individuals with moderate hyperphagia: would expect most to achieve mild hyperphagia with a proportion achieving no hyperphagia.

Hope this is of some help. Delighted to discuss any of the above in more detail.

Best wishes

Dimitri

NICE National Institute for Health and Care Excellence

From: Nicky Welton
Sent: Wednesday, October 18, 2023 1:44 PM
To: Celia Mayers ; Elsa Marques ;Jelena Savovic ;Deborah Caldwell
Cc: Emma Douch
Subject: RE: Company points on key issues: Obesity and hyperphagia (Bardet-Biedl syndrome) - setmelanotide [ID3947]

Hi Celia,

Thanks for sending the clinicians responses to this question.

1. The first point to note is that the data we had from the company on the more granular BMI class shifts were in patients who were "BBS patients aged <18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients)." The companys data therefore suggests that there are a group of patients who will be considered to have responded to setmelanotide and are included in the modelling, but who would not achieve a BMI-Z class shift with the more granular definition.
2. We do not have data on patients hyperphagia state, but we have heard that from the company that patients would not be expected to achieve BMI-Z reduction without having reduced hyperphagia. We have therefore used the BMI-Z class shift data as a proxy to estimate change in hyperphagia, but acknowledge this is very uncertain.
3. Both clinical experts highlight the lack of data and uncertainty in the change in hyperphagia, which we agree with.
4. Dimitri answered the question in relation to change in BMI-Z class.
   a. For those with BMI-Z > [redacted] class change, Dimitri states that most move to mild and a proportion to none, regardless of initial hyperphagia severity. In the EAG preferred assumptions, we assuming all move to mild hyperphagia. This is consistent with Dimitri's view, although we do not have a proportion moving to no hyperphagia. Dimitri does not give a proportion that would move to no hyperphagia, but does say most will move to mild, as assumed in the EAG base-case.
   b. For those with BMI-Z< [redacted] class change, Dimitri states that for those with severe hyperphagia initially, then most will move to moderate and a proportion to mild. For those with moderate hyperphagia initially, most move to mild and a proportion to none. This view that there would be a change in hyperphagia without any change in BMI-Z is because these patients are responders. The EAG has assumed that those without a change in BMI-Z class would also be those patients with a minimal change in hyperphagia (otherwise BMI-Z would be expected to fall). Although we agree that if a patient has been determined a responder, then an improvement in both BMI-Z and hyperphagia would be a reasonable assumption, the company's data shows that there is a subgroup of patients who were classed as responders at 52 weeks who did not change BMI-Z class, which seems to contradict that. Our base-case assumption is based on this data, provided by the company. We have run a scenario where those with no BMI-Z class shift move from Severe to Moderate, and from Moderate to Mild hyperphagia as suggested by Dimitri (uploaded via NICEDocs). However, note the EAG prefers the assumptions used in its base-case.
5. Elizabeth does not answer the question in relation to BMI-Z changes, but gives an overall response that patients who are responders would move from severe or moderate hyperphagia to mild or no hyperphagia. It does not seem plausible to us that patients who achieve no change in BMI-Z class would move from severe hyperphagia to mild or no hyperphagia. We therefore feel that the BMI-Z class change information, whilst

uncertain, is the best proxy we have for changes in hyperphagia, given the company did not measure hyperphagia in their trial.

We will upload the additional scenario mentioned above to NICE Docs.

Best wishes,

Nicky, Elsa, Debbi

BRISTOL TAG
EVIDENCE FOR DECISION MAKERS

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG Additional Scenario following Expert Comments post-ECM2

Produced by: Bristol Technology Assessment Group, University of Bristol

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/57/96.

Declared competing interests of the authors: None of the Bristol TAG authors have any conflicts of interest to declare.

[redacted]

ABBREVIATIONS

Abbreviation	Definition
EAG	Evidence Assessment Group
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

1 INTRODUCTION

Following comments from clinical experts set to the EAG on 17th Oct 2023 post-ECM2, the EAG has provided a scenario for an alternative change in hyperphagia from severe hyperphagia at baseline, using the EAG base-case presented at ECM2 with the number of adult carers set to 1 (as requested by the committee).

2 MODEL ASSUMPTIONS

The EAG base-case model is described in section 5.2 of the EAG response to consultation comments for ECM2, summarised below with the change in adult carers requested by the committee.

The EAG's preferred assumptions are:

1. Initial severity of hyperphagia where 60% of patients have severe hyperphagia, and 40% have moderate hyperphagia
2. Treatment effect on hyperphagia with [redacted] of severe moving to mild and [redacted] to moderate, and [redacted] of moderate moving to mild
3. Treatment effect on BMI-Z an average class reduction of [redacted] for the paediatric BBS population
4. Number of caregivers for adults set to 1.0
5. Baseline utilities from Riazi et al. as described in Key issue 10 of the companys technical engagement response, with the EAG's corrected BBS utility multiplier of [redacted] (see EAG response to the companys technical engagement comments).

2.1 Additional Scenario

The EAG received comments from clinical experts suggesting that those who did not achieve a class-shift in BMI-Z would still have a reduction in hyperphagia because they are classed as responders. The EAG note that the BMI-Z class shift data provided by the company includes only patients who were responders "BBS patients aged <18 years who were classified as 52 week responders (Study RM-493-023, pivotal patients)", and so it seems there is a subgroup

of responders who do not have a BMI-Z class shift, and it seems implausible that these patients would have a large reduction in hyperphagia without a corresponding change in BMI-Z class using the company's more granular definition. However, we have run an additional scenario where [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia, and [redacted] of moderate move to mild. Results are shown for the paediatric population in Table 1 and the mixed (60% paediatric, 40% adult) population in Table 2.

3 QALY Weighting

In the companys updated base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the EAG base-case at ECM2 with 1 carer per adult patient, the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). The EAG base-case at ECM2 with 1 carer per adult patient would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

In the scenario where Scenario with [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia applied to the at ECM2 with 1 carer per adult patient, the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric), corresponding to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

TABLE 1 COST-EFFECTIVENESS RESULTS FOR A SCENARIO ANALYSIS WITH [redacted] OF SEVERE HYPERPHAGIA PATIENTS MOVE TO MILD AND [redacted] MOVE TO MODERATE HYPERPHAGIA APPLIED TO THE EAG BASE-CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£231,902
Scenario with [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£218,575

TABLE 2 COST-EFFECTIVENESS RESULTS FOR A SCENARIO ANALYSIS SCENARIO WITH [redacted] OF SEVERE HYPERPHAGIA PATIENTS MOVE TO MILD AND [redacted] MOVE TO MODERATE HYPERPHAGIA APPLIED TO THE EAG BASE-CASE AT ECM2 WITH 1 CARER PER ADULT PATIENT: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case at ECM2 with 1 adult carer							
BSC	[redacted]	[redacted]	[redacted]				
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,259
Scenario with [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£224,272

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

New value proposition following ECM2

17th November 2023

We thank NICE, the Committee Chair, the Committee, the EAG, clinical experts and BBSUK for their continued collaboration and dialogue to make setmelanotide accessible to BBS patients living with obesity. This collaboration and dialogue have been and continue to be very much appreciated.

We have heard from NICE, clinical experts and patients that there is strong support for setmelanotide to be available to a broader population than proposed in our initial submission (BBS patients living with obesity and severe hyperphagia). We agree it would be beneficial to facilitate this and submit this revised value proposition with an updated base-case and increased Patient Access Scheme (PAS) to [redacted]% to enable setmelanotide access for its full indication (treatment of obesity and the control of hunger associated with genetically confirmed BBS in adults and children 6 years of age and above).

Following discussions with NICE since the ECM2, we are in alignment with all the Committee's preferred assumptions, except the baseline hyperphagia severity distribution of treated patients (see summary of updated base-case assumptions below), which misrepresents the setmelanotide target population.

In assessing our updated base-case, we would kindly ask the Committee to take into consideration:

1. The updated PAS
2. Our calculation for baseline hyperphagia severity distribution in the setmelanotide treated population (BBS patients with obesity)
3. The conservative nature of the model, which underestimates the quality of life benefits and savings from treatment with setmelanotide
4. The revised base-case and scenario analyses

1. Updated PAS

To ensure patient access to setmelanotide's labelled indication (treatment of obesity and the control of hunger associated with genetically confirmed BBS in adults and children 6 years of age and above) we propose to increase the PAS to [redacted]%. With this improved PAS setmelanotide can be considered cost-effective if the Committee accept the revised base-case (section 4), which is closely aligned to the Committee's preferred base-case except for the baseline hyperphagia severity distribution (section 2).

2. Baseline hyperphagia severity in the setmelanotide treated population (BBS patients with obesity)

We acknowledge that there is uncertainty in the estimates for the baseline hyperphagia severity in the setmelanotide treated population (BBS patients living with obesity) due to lack of a clear definition of the patient population within the source data.

The uncertainty arises from a lack of clarity as to whether the previously discussed assumption of 60% severe and 40% moderate hyperphagia distribution, quoted by clinical experts and ourselves applies to the general BBS population or only to BBS patients living with obesity. We acknowledge that within our company submission and responses to the EAG it was unclear to which population this assumption applied and we must base our assumptions on accurate data; hence, to clarify this, we contacted BBSUK to clarify the data.

BBS UK confirmed that the 60/40 distribution originates from a 2022 survey of BBS UK members (general BBS patients, not only BBS UK members living with obesity), 60% responded that they are living with severe.

"... we circulated a questionnaire (qualitative) amongst our patient population last year, asking about the impact of hyperphagia.... Of those who responded:

60% were considered as having severe hyperphagia

40% were considered as having moderate hyperphagia "

In another survey to its BBS UK members, conducted in 2020/21 in the general BBS population, 70% responded that they experienced moderate or severe obesity. (https://bbsuk.org.uk/bbs-uk-publications/bbs-uk-membership-survey/). This aligns with the findings of Pomeroy 2021, which we included in our letter of the 25th of September regarding inaccuracies (page 3), which estimated that 70% of children with BBS are living with obesity. As both BBS UK surveys were conducted in BBS UK members, these data can be combined to estimate the share of BBS patients living with obesity that have severe hyperphagia in the UK.

Clinical experts agree that all patients with severe hyperphagia cannot control their food intake and, therefore, will be living with obesity. This lack of control leads to the proportion of BBS patients living with obesity being 86% of patients with severe hyperphagia and 14% of patients with moderate hyperphagia (please see the diagram below), as previously stated in our letter of the 25th of September regarding inaccuracies (page 3).

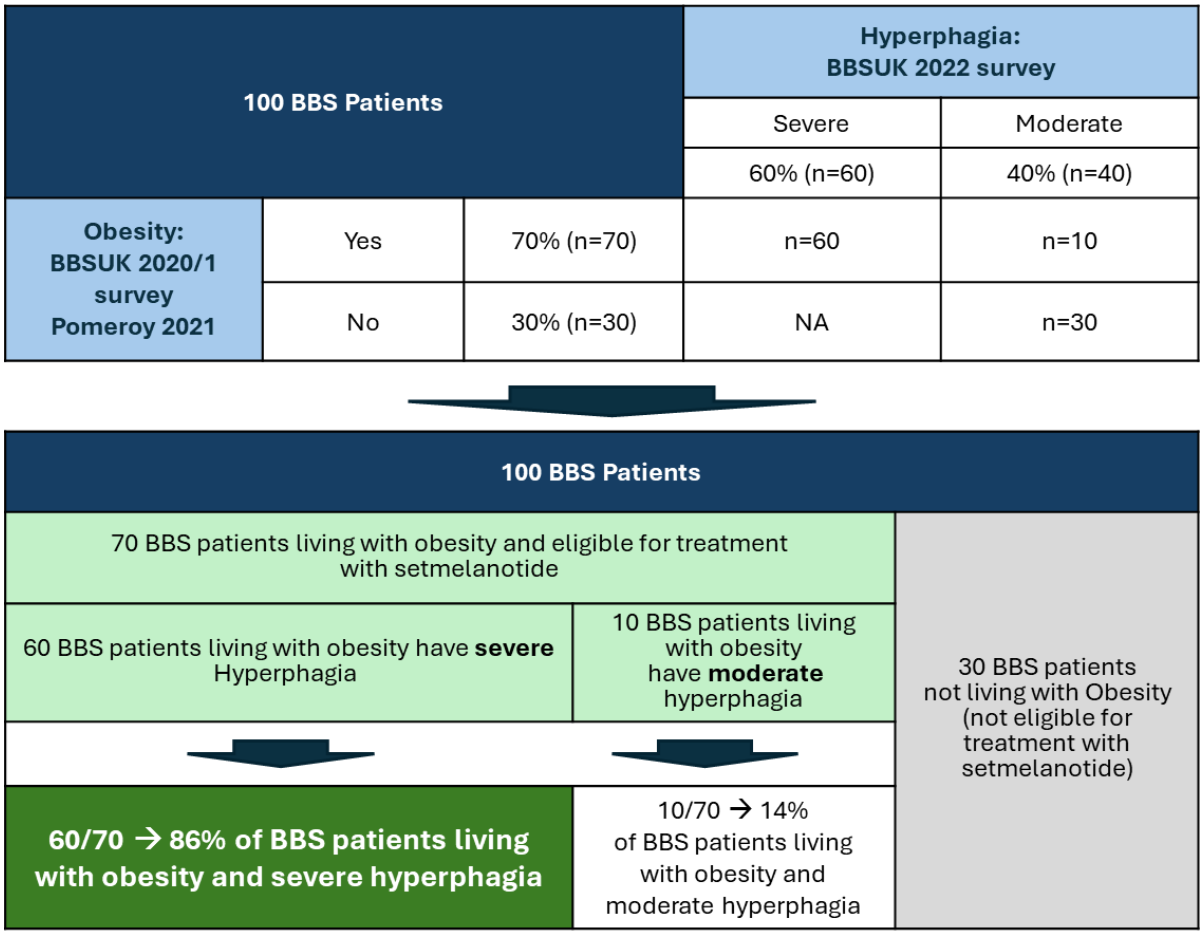

Figure 1. Illustration of obesity and hyperphagia distribution in the general BBS population.

Testimony from Mr Dimitri Pournaras further supports the use of the above baseline severity distribution, as he stated in the response to the BMI-Z score query that *"The **vast majority of patients will have severe hyperphagia as it will be these patients who will present more frequently to any healthcare professionals, more likely to be referred to specialist services** if already known to healthcare professionals and **more likely to be prioritised for treatment** if already in services."*

Based on the above clarifications, it can be seen that the baseline composition of patients treated with setmelanotide is more accurately represented by 86% severe and 14% moderate hyperphagia, and thus used in our revised base-case. Applying this ratio to responders in the model is considered conservative, as the responder population treated beyond 14 weeks is likely to consist of a greater proportion of patients with severe hyperphagia. This was acknowledged by the EAG in their critique of our response to the DG (5th September, page 3).

3. The economic model is conservative

As we have stated in our response to the DG, and the EAG have agreed, the economic model is conservative. The main assumptions in which the model is conservative are:

a. Limited list of co-morbidities associated with early-onset obesity
b. Number of caregivers for adult patients
c. Hyperphagia treatment effect
d. Treatment effect after discontinuation
e. Upper limit of BMI-Z class (>4)
f. Rate of obesity-related comorbidities in early-onset obesity

Together, these conservative assumptions have an additive impact on the ICER and undiscounted QALYs.

a. Limited list of co-morbidities associated with early-onset obesity

To keep the model manageable and to avoid potential double counting, many comorbidities associated with early-onset obesity, such as dyslipidaemia, anxiety, depression, asthma, dermatological complications, cancer, dysfunctions of the reproductive system (e.g. PCOS, polycystic ovary syndrome), infections and GERD (gastroesophageal reflux disease) were not included in the model. As agreed by the EAG in their critique of our response to the DG (5th September, page 8), this results in the model underestimating the improvements in patients' quality of life. The model also underestimates the reduction in costs associated with these comorbidities resulting from the reduction of obesity with setmelanotide, leading to a higher ICER and lower incremental undiscounted QALYs.

b. Number of caregivers for adult patients

In the revised base-case we are aligned with the Committee's preferred assumption for caregivers for adults (1 caregiver). However, based on clinical expert opinion slide 53 in of ACM1 lead team presentation draft v0.8 for committee) there are 1-2 carers per adult patient and EAG research identified 0-2 caregivers per adult patient (slide 53 in of ACM1 lead team presentation draft v0.8 for committee – note there is a typo as it states that range is 0-20), we consider that the number of caregivers in the model underestimates the actual number.

Acknowledging that in current clinical practice, with best supportive care, patients with moderate hypergraphia may require fewer carers (we assume [redacted]) compared with the number of carers for patients with severe disease (we assume [redacted]), we include a scenario with [redacted] caregivers, which shows a decrease in the ICER and an increase in incremental undiscounted QALYs (see scenario 1 in Table 1).

c. Hyperphagia treatment effect

The model does not account for patients who move to no hyperphagia, thus underestimating the benefit of setmelanotide. Patient testimonies support that some patients would move to no hyperphagia. In their critique of our DG response (5th September, page 8), the EAG agreed that "***there may be some patients whose hyperphagia is completely eliminated"***. Also, in response to the BMI-Z score query, clinical experts confirm that some patients would move to no hyperphagia:

- Dr. Dimitri Pournaras stated that *"Individuals with severe hyperphagia what a reduction of BMI-Z score >2: would expect most of them to achieve mild, with **a proportion to achieve no hyperphagia** as the group has had a great response to the treatment in terms of weight loss maintenance. [...] Individuals with moderate hyperphagia: would expect most to achieve mild hyperphagia with **a proportion achieving no hyperphagia**."*
- Dr. Elizabeth Forsythe stated [...] *"it was clear that the patients who responded to treatment appeared to have a **significant effect on their hunger and hyperphagia consistent with what I would interpret as a move from severe or moderate hyperphagia to mild or no hyperphagia**. This translated into an improvement in quality of life."*

Thus, the benefit of setmelanotide is underestimated by not accounting for the patients moving to no hyperphagia, which leads to lower incremental undiscounted QALYs and higher ICER.

d. Treatment effect after discontinuation

In the model, setmelanotide non-responders who discontinue treatment at 14 weeks are assumed to experience no treatment effect during Year 1. Patients discontinuing treatment after 52 weeks, are also assumed to lose treatment effect at the time of discontinuation. However, in clinical practice, both sets of patients will continue to accrue benefits for several months after discontinuation (tapering of the benefit). Thus, we consider that the benefit of setmelanotide is underestimated in the economic model leading to lower incremental undiscounted QALYs.

The EAG noted in their critique of our DG response (5th September, page 7) that they agreed with this, but this may be outweighed by the model assumption that the benefit of setmelanotide does not wane in the long-term. However, we note that the model also does not account for the natural progression of the untreated patients' weight which we heard from clinical experts during ECM1 would continue to increase if not treated. Hence, we maintain that the model underestimates the benefit of setmelanotide, leading to lower incremental undiscounted QALYs and an increase in ICER.

e. Upper limit of BMI-Z class (>4)

To align with the BMI-Z ranges for which comorbidity data and impact on mortality data were available, the upper limit of BMI-Z classes included in the model was BMI-Z >4. However, we note that this would underestimate the risks in patients with an extremely high BMI-Z (in the RM-493-023 trials there were patients with BMI-Z of 5.5 or 7) and as the EAG agreed in their critique of our DG response (5th September, page 8), "*the **BMI-Z / BMI categories used are likely to underestimate the benefits** for patients with extremely high BMI / BMI-Z*." This would lead to underestimating undiscounted incremental QALYs and hence increasing the ICER.

f. Rate of obesity-related comorbidities in early-onset obesity

As mentioned in our response to the DG, the EOObesity-model commissioned by us and whose data we submitted with the response, showed that the impact of early-onset obesity on comorbidities and mortality in untreated patients was markedly greater than that assumed in the base-case. We also showed that incorporating the updated estimates for mortality and comorbidities led to life year and QALY gains, indicating that these are underestimated in the economic model.

4. Revised base-case and scenario analyses

We submit an updated base-case and scenario analyses (Table 1) based on a proposed updated simple discount of [redacted]%, which is at the absolute limit of what we can offer while remaining commercially viable in the UK. This updated base-case aligns with the Committee's preferred assumptions, except for the baseline hyperphagia severity distribution. For completeness, we include previously used scenarios for baseline hyperphagia distributions of 75% severe and 25% moderate.

Summary of updated base-case assumptions

- Mixed population of 60% children and 40% adults
- *Baseline population of 86% severe hyperphagia and 14% moderate hyperphagia patients*
- [redacted]% of severe hyperphagia patients move to mild and [redacted]% move to moderate hyperphagia, and [redacted]% of moderate hyperphagia patients move to mild
- Treatment effect on BMI-Z is an average class reduction of [redacted] for the paediatric BBS population
- 1% discontinuation rate
- Utility values for BMI or BMI-Z class health states from the literature
- BBS multiplier calculated by the EAG using corrected mapping from the PedsQL scores in RM 493-023
- 1 caregiver per adult patient
- Ongoing weight management in local secondary care weight management clinics

Table 1: Revised base-case and scenario analyses results with updated PAS (probabilistic results for mixed population)

	Incremental costs	Incremental QALYs	Incremental undiscounted QALYs	ICER
Base-case	[redacted]	[redacted]	[redacted]	**£152,193**
Scenario 1 Caregivers for adult patients: [redacted]	[redacted]	[redacted]	[redacted]	£149,418
Scenario 2 Baseline hyperphagia: 75% severe and 25% moderate	[redacted]	[redacted]	[redacted]	£159,230

The revised base-case ICER for the mixed population of £152,193 (Table 1) is within the cost-effectiveness threshold when the [redacted] QALY weighting is considered. Due to the conservative nature of the model, it is highly likely that the base-case ICER has been overestimated and the incremental undiscounted QALYs have been underestimated. We request, that as contemplated in section 6.2.34 of the NICE health technology evaluations: the manual, the Committee may be able to accept a higher degree of uncertainty in this updated base-case for setmelanotide which is an innovative therapy for a rare disease in a predominantly paediatric population where there are significant unmet needs.

Conclusion

To enable access to setmelanotide for the full adult and paediatric initiated BBS patients living with obesity, we have adjusted our base-case and PAS, and are prepared to approach PASLU to update the PAS to the discount proposed herein.

We request that, as setmelanotide is an innovative therapy for a rare disease in a predominantly paediatric population, the Committee take into consideration the conservative nature of the model and be able to accept a higher degree of uncertainty in this updated base-case to facilitate access for BBS patients with obesity.

If the Committee does not consider the new proposed base-case cost-effective, but considers paediatric initiation or severe hyperphagia only as viable options, we would propose updating the PAS accordingly to demonstrate cost-effectiveness for these populations.

We thank NICE, the Committee Chair, the Committee, the EAG and clinical experts in advance for taking the time to consider this new value proposition.

We look forward to their views and a way to finalise the setmelanotide assessment.

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG Response to New value proposition following ECM2

Produced by: Bristol Technology Assessment Group, University of Bristol

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[redacted]

1 ABBREVIATIONS

Abbreviation	Definition
BBS	Bardet-Biedl syndrome
BMI	Body Mass Index
BMI-Z	Body Mass Index Z score
EAG	Evidence Assessment Group
ECM	Evaluation Committee Meeting
HRQoL	Health-Related Quality of Life
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
PAS	Patient Access Scheme
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

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2 INTRODUCTION

This report provides the evidence assessment group (EAG) review of the revised value proposition with updated base-case provided by Rhythm Pharmaceuticals (company) dated 17th November 2023. The company has provided an updated base-case, scenario analyses, and has updated its simple discount patient access scheme (PAS).

3 REVIEW OF COMPANY'S REVISED VALUE PROPISITION

3.1 Updated Patient Access Scheme (PAS)

The company has updated its simple discount patient access scheme for setmelanotide to [redacted]. All of the results provided in this report use the updated PAS price.

3.2 Baseline hyperphagia severity in the setmelanotide treated population (BBS patients with obesity)

The company have clarified with BBS UK that the estimates of 60% severe hyperphagia and 40% moderate is for the full BBS population, and not just in those with obesity as implied in the company's submission and assumed by the EAG. They combine that information with the proportions with moderate or severe obesity to estimate 86% and 14% BBS patients with obesity for severe and moderate hyperphagia respectively in clinical practise, and this is what is used in the companys updated base-case. The company provided a scenario where the split is 75% severe and 25% moderate hyperphagia.

The companys calculations are correct under the following assumptions:

1. The population surveyed was the same in the surveys for obesity and hyperphagia
2. Responders to both surveys are representative of the full BBS population
3. All severe hyperphagia patients have moderate/severe obesity
4. None of the BBS population have mild hyperphagia, so that all of the patients with mild/no obesity have moderate hyperphagia

The EAG agrees that the assumption that all severe hyperphagia patients will have moderate/severe obesity is reasonable. However, based on Figure 1 of the companys post-ECM2 submission 75% of patients with moderate hyperphagia would have mild or no obesity, which the EAG finds unlikely given the definition of moderate hyperphagia provided by the company. This could be explained if the survey for obesity included patients with mild hyperphagia who did not have moderate/severe obesity, which would then give a higher proportion of patients with moderate hyperphagia and moderate/severe obesity. For example, suppose we had the following hypothetical cohort of patients shown in Table 1.

TABLE 1 HYPOTHETICAL COHORT OF BBS PATIENTS CONSISTENT WITH RESULTS FROM BBS UK SURVEYS

		Hyperphagia			
		Severe	Moderate	Mild	Total
Obesity	Yes	60	20	0	80
	No	0	20	10	35
	Total	60	40	10	115

These figures would be consistent with the results reported from the surveys if the obesity survey included those with mild hyperphagia but the hyperphagia survey did not, but the proportion of patients with obesity that have severe hyperphagia would be 75% rather 86%.

The EAG considers the estimates of baseline hyperphagia in the BBS population with obesity to be highly uncertain. The proportion with severe hyperphagia may be higher than the 60% assumed in the EAG base-case (which assumed that the hyperphagia survey was on BBS patients with obesity), but likely lower than 86% based on face-validity of the implied proportion of moderate hyperphagia patients with obesity. The EAG therefore considers the company scenario with 75% with severe hyperphagia at baseline to be more plausible that the company's base-case with 86% severe.

3.3 Conservative nature of the model

The Company outline six areas where they feel their model is conservative:

a. Limited list of co-morbidities associated with early-onset obesity.

   As noted in the EAG response to the companys comments on the DG, the EAG agrees that not all co-morbidities associated with obesity have been included in the model, and this may under-estimate HRQoL benefits.

b. Number of care-givers for adult BBS patients. The company has updated the base-case assumptions to 1 caregiver for adults in alignment with the committee's preferred assumption.

   The EAG is recognises the number of caregivers per adult patient will in practice vary depending on the co-morbidity burden, and that there is uncertainty in the average number of caregivers. The EAG is content that the company's updated base-case is in line with the committees preferences.

c. Hyperphagia treatment effect. The company's model assumes that all patients move to mild hyperphagia, but in practice some may move to "no hyperphagia" and receive increased utility benefits. The company presents testimony from clinical experts in support of this.

   As noted in the EAG response to the companys comments on the DG, the EAG agrees that there may be some patients whose hyperphagia is completely eliminated, but there will also be patients who move to moderate rather than mild hyperphagia. It can be

seen from the hunger scores collected in RM-493-023 that there is variability across patients. It is therefore not clear to the EAG that there will be a net under-estimation of utility benefits.

d. Treatment effect after discontinuation. The company point out that patients who discontinue setmelanotide immediately return to their state at baseline, when in fact they will experience a tapering of the benefit in practise. Furthermore the model does not account for the natural progression of the untreated patients' weight which would continue to increase if not treated.

   As noted in the EAG response to the companys comments on the DG, whilst the EAG agree that this is true, the company's model also assumes that the benefits of setmelanotide continue into the long-term without waning, which is likely to over-estimate the benefits of setmelanotide, and may outweigh the effects of not including a tapering effect in those who discontinue. The company is right that the model does not account for the natural progression of untreated patient's weight, but it also does not account for natural progression in weight for those who are treated. So, the EAG does agree that the model may be conservative in this respect, but the magnitude of the effect is unclear.

e. Upper limit of BMI-Z class (>4). The company note that in RM-493-023 there were patients with extremely high (BMI / BMI-Z of 5.5 or 7), but their model does not capture the comorbidity and mortality benefits for patients with very high BMI / BMI-Z.

   As noted in the EAG response to the companys comments on the DG, the EAG have agreed that the BMI-Z / BMI categories used are likely to underestimate the benefits for patients with extremely high BMI / BMI-Z.

f. Rate of obesity-related comorbidities in early-onset obesity. The EOObesity data model predicts a lower life expectancy for untreated patients, and when this is included in the companys model predicts higher QALY gains.

   As noted in the EAG response to the companys comments on the DG, the EAG are supportive of using estimates of the impact of obesity on comorbidities based on an appropriate population (early-onset obesity), rather than utilising data from adults with obesity. However, it is not clear to the EAG how much of the model inputs were derived from data on children. The EAG did not have the resources to review this work in detail, but had concerns about generalisability to a UK population.

4 COMPANY's UPDATED ANALYSES

The company has provided results from their an updated base-case which assumes:

- Mixed population of 60% children and 40% adults
- *Baseline population of 86% severe hyperphagia and 14% moderate hyperphagia patients*

- [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia, and [redacted] of moderate hyperphagia patients move to mild
- Treatment effect on BMI-Z is an average class reduction of [redacted] for the paediatric BBS population
- 1% discontinuation rate
- Utility values for BMI or BMI-Z class health states from the literature
- BBS multiplier calculated by the EAG using corrected mapping from the PedsQL scores in RM 493-023
- 1 caregiver per adult patient
- Ongoing weight management in local secondary care weight management clinics

The company ran the following scenarios:

- Scenario 1: Caregivers for adult patients: [redacted]
- Scenario 2 Baseline hyperphagia: 75% severe and 25% moderate

Note that the "EAG-corrected mapping from the PedsQL scores scores in RM 493-023" preferred by the committee in response to Key Issue #10 at technical engagement calculated a BBS multiplier of [redacted]. We assume this is what the company have used in their updated base-case.

The EAG agree that the company's updated base-case represents the committee's preferred assumptions, with the exception of the proportion in the severe/moderate hyperphagia states at baseline, as discussed in section 3.2 above, and therefore prefer the company's Scenario 2. The EAG's base-case previously assumed the treatment effect on hyperphagia with [redacted] of patients moving to mild, and [redacted] to moderate, [redacted] moderate to mild, and we provide a scenario analysis with these proportions applied.

A copy of the model with the company's updated base-case was not made available for our review. We have implemented the company's updated base-case and scenarios with the new PAS in the copy of the company's model made available to us prior to ECM2, however were unable to exactly replicate the results reported in the company's submission. We give the results we obtained below based on a simulation sample size of 10,000 iterations. All results shown are from a probabilistic analysis.

The results from the company's updated base-case and scenarios obtained by the EAG are shown for the paediatric population in Table 2 and for the mixed (60% paediatric, 40% adult) population in Table 3.

TABLE 2 COST-EFFECTIVENESS RESULTS FOR THE COMPANY'S UPDATED BASE AND SCENARIOS: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£151,235
Companys Scenario 1 ([redacted]_carers for adult patients)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£146,763
Companys Scenario 2 (Initial severity of hyperphagia 75% severe and 25% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£157,330

TABLE 3 COST-EFFECTIVENESS RESULTS FOR THE COMPANY'S UPDATED BASE AND SCENARIOS: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£155,436
Companys Scenario 1 ([redacted] carers for adult patients)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£149,897
Companys Scenario 2 (Initial severity of hyperphagia 75% severe and 25% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£161,596

4.1 Additional Scenarios

We run a scenarios using the baseline hyperphagia distribution of 60% severe and 40% moderate assumed in the EAG's previous base-case, which reflects the committees preferred assumptions following ECM2. The EAG's previous base-case assumed the treatment effect on hyperphagia with [redacted] of patients moving to mild, and [redacted] to moderate, [redacted] moderate to mild, which we provide here as a scenario analysis. These scenarios are shown for the paediatric population in Table 4 and the mixed (60% paediatric, 40% adult) population in Table 5.

TABLE 4 COST-EFFECTIVENESS RESULTS FOR ADDITIONAL SCENARIOS APPLIED TO THE COMPANY'S UPDATED BASE-CASE: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Committees preferred assumptions following ECM2 (Companys updated base-case with Initial severity of hyperphagia 60% severe and 40% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,676
Company's updated base-case Scenario 2 + Treatment effect on hyperphagia with [redacted] of patients moving to mild, and [redacted] to moderate, [redacted] moderate to mild							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£167,418

TABLE 5 COST-EFFECTIVENESS RESULTS FOR AN ADDITIONAL SCENARIOS APPLIED TO THE COMPANY'S UPDATED BASE-CASE: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Committees preferred assumptions following ECM2 (Companys updated base-case with Initial severity of hyperphagia 60% severe and 40% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£171,091
Company's updated base-case Scenario 2 + Treatment effect on hyperphagia with [redacted] of patients moving to mild, and [redacted] to moderate, [redacted] moderate to mild							

BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£172,014

5 QALY Weighting

In the companys updated base-case the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). In the companys updated base-case Scenario 2 (for initial severity of hyperphagia) the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). Whilst all these figures are uncertain and based on strong assumptions, the EAG considers that it is plausible that a QALY weighting applies. The company's updated base-case would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population. The EAGs preferred estimate (Scenario 2) would correspond to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population.

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Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG base-case (companys scenario 2) from ECM3

Produced by: Bristol Technology Assessment Group, University of Bristol

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[redacted]

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LIST OF TABLES

ABBREVIATIONS

Abbreviation	Definition
BBS	Bardet-Biedl syndrome
EAG	Evidence Assessment Group
ECM	Evaluation Committee Meeting
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
PAS	Patient Access Scheme
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

1 INTRODUCTION

The committee's preferred base-case aligns with the EAG base-case presented at ECM3, which is the same as the companys Scenario 2 at ECM3. The EAG has been asked to apply 90% of the QALY weight to reflect the uncertainty in the evidence, which we provide in this document. All of the results provided use the simple discount patient access scheme for setmelanotide of [redacted].

2 EAG Base case

The EAG agreed that the companys updated base-case provided on 17th November 2023 represents the committee's preferred assumptions, with the exception of the proportion in the severe/moderate hyperphagia states at baseline, and therefore preferred the companys Scenario 2.The assumptions are as follows:

- Baseline hyperphagia: 75% severe and 25% moderate (Scenario 2)

- [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia, and [redacted] of moderate hyperphagia patients move to mild
- Treatment effect on BMI-Z is an average class reduction of [redacted] for the paediatric BBS population
- 1% discontinuation rate
- Utility values for BMI or BMI-Z class health states from the literature
- BBS multiplier of [redacted]
- 1 caregiver per adult patient
- Ongoing weight management in local secondary care weight management clinics

The results from the companys updated base-case and scenario2 preferred by the EAG are shown for the paediatric population in Table 1 and for the mixed (60% paediatric, 40% adult) population in Table 2.

TABLE 1 COST-EFFECTIVENESS RESULTS FOR THE COMPANYS UPDATED BASE-CASE AND EAG BASE-CASE (COMPANY SCENARIO2): PAEDIATRIC POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£151,235
EAG Base-case (Company Scenario 2: Initial severity of hyperphagia 75% severe and 25% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£157,330

TABLE 2 COST-EFFECTIVENESS RESULTS FOR THE COMPANYS UPDATED BASE-CASE AND EAG BASE-CASE (COMPANY SCENARIO2): MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
Companys updated base-case							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£155,436
EAG base-case (Company Scenario 2: Initial severity of hyperphagia 75% severe and 25% moderate)							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£161,596

3 QALY Weighting

In the EAGs base-case (the companys updated base-case Scenario 2 for initial severity of hyperphagia), the probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population and [redacted] for the mixed population (60% paediatric). This corresponds to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population, and a weighting of [redacted] and corresponding threshold of [redacted] in the mixed population. Whilst all these figures are uncertain and based on strong assumptions, the EAG considers that it is plausible that QALY weighting applies. The weighted ICERs for the EAG base-case (company scenario 2) are presented in Table 3 for the paediatric and the mixed (60% paediatric, 40% adult) populations. Given the uncertainty in the evidence the committee requested the ICERs with 90% of the usual QALY weighting applied, these are presented in Table 3.

TABLE 3 WEIGHTED COST-EFFECTIVENESS RESULTS FOR THE EAG BASE-CASE (COMPANY SCENARIO2): PAEDIATRIC AND MIXED (60% PAEDIATRIC, 40% ADULT) POPULATIONS (PROBABILISTIC RESULTS)

	Incremental Costs	Incremental undiscounted QALYs	ICER	Weighted ICER	90% of QALY weighting applied to ICER
Paediatric population	[redacted]	[redacted]	£157,330	[redacted]	[redacted]
Mixed population (60% paediatric, 40% adult)	[redacted]	[redacted]	£161,596	[redacted]	[redacted]

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome: A Highly Specialised Technology Evaluation [ID3947]

EAG Response to request for additional analyses following ECM3

Produced by: Bristol Technology Assessment Group, University of Bristol

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[redacted]

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ABBREVIATIONS

Abbreviation	Definition
BBS	Bardet-Biedl syndrome
EAG	Evidence Assessment Group
ECM	Evaluation Committee Meeting
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
NIHR	National Institute for Health and Care Research
PAS	Patient Access Scheme
QALY	Quality-Adjusted Life Year
TAG	Technology Assessment Group

1 Introduction

This report provides updated results requested by NICE on 07 February 2024. Rhythm Pharmaceuticals (the company) submitted a request to consider an optimised recommendation in children and young adults (up to age 18) only, and updated its simple discount patient access scheme for setmelanotide to [redacted]. NICE asked the EAG to provide results for the EAG and Company base-case assumptions from ECM3 in paediatric and mixed populations. All of the results provided in this report use the updated PAS price. The company have not presented any new evidence.

2 ECM3 EAG and Company base-case assumptions

At ECM3 the company and EAG base-cases only differed in the assumed baseline distribution of hyperphagia. The EAG assumed a 75% severe and 25% moderate split whereas the company assumed a 84% severe and 16% moderate split. All other assumptions were the same:

- Treatment effect on hyperphagia: [redacted] of severe hyperphagia patients move to mild and [redacted] move to moderate hyperphagia, and 100% of moderate hyperphagia patients move to mild
- Treatment effect on BMI-Z: average class reduction of [redacted] for the paediatric BBS population
- Discontinuation rate: 1%
- Utility values for BMI or BMI-Z class health states from the literature
- BBS multiplier: [redacted]
- Carers per adult patient: 1
- Ongoing weight management in local secondary care weight management clinics

Subsequently to ECM3, in their request for an optimised recommendation in children and young adults (up to age 18) only, the company apply the EAG base-case baseline hyperphagia distribution of 75% severe and 25% moderate in the paediatric initiation population.

3 ECM3 Base-case results updated with new PAS discount

We applied the companys updated PAS discount to the EAG and Company base-cases from ECM3 for the paediatric initiated population (Table 1) and the mixed (60% paediatric, 40% adult) population (Table 2). All results shown are from a probabilistic analysis with a simulation sample size of 10,000 iterations.

TABLE 1 COST-EFFECTIVENESS RESULTS FOR THE EAG AND COMPANY BASE CASES FROM ECM3 WITH THE UPDATED PAS DISCOUNT APPLIED: PAEDIATRIC POPULATION (PROBABILISTIC RESULTS). NOTE COMPANYS UPDATED BASE-CASE FOLLOWING ECM3 IN THEIR CASE FOR AN OPTIMISED RECOMMENDATION MATCHES THE EAG BASECASE AT ECM3

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case (75:25 severe:moderate hyperphagia at baseline) at ECM3 with updated PAS discount applied. Note this is the companys updated base-case following ECM3 in their case for an optimised recommendation							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,638
Companys base-case at ECM 3 (84:16 severe:moderate hyperphagia at baseline) with updated PAS discount applied							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,165

TABLE 2 COST-EFFECTIVENESS RESULTS FOR THE EAG BASE-CASE AND COMPANYS BASE-CASE FROM ECM3 WITH THE UPDATED PAS DISCOUNT APPLIED: MIXED (60% PAEDIATRIC, 40% ADULT) POPULATION (PROBABILISTIC RESULTS)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER
EAG base-case (75:25 severe:moderate hyperphagia at baseline) at ECM3 with updated PAS discount applied							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£174,904
Companys base-case at ECM 3 (84:16 severe:moderate hyperphagia at baseline) with updated PAS discount applied							
BSC	[redacted]	[redacted]	[redacted]				
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,658

4 QALY Weighting

4.1 Paediatric initiation

The probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the paediatric population for the EAGs base-case at ECM3 with 75:25 baseline hyperphagia split (also companys base-case following ECM3). This corresponds to a weighting of [redacted] and corresponding threshold of [redacted] in the paediatric population. In the companys base-case from ECM3 (84:16 baseline hyperphagia split) the undiscounted incremental QALY gain for setmelanotide is [redacted] corresponding to a weighting of [redacted] and threshold of [redacted].

Given the uncertainty in the evidence the committee requested the ICERs with 90% of the usual QALY weighting applied, these are presented in Table 3.

4.2 Mixed population (60% paediatric)

The probabilistic undiscounted incremental QALY gain for setmelanotide is [redacted] for the mixed population (60% paediatric) using the EAGs base-case at ECM3 (75:25 baseline hyperphagia split), and [redacted] using the Companys base-case from ECM3 (84:16 baseline hyperphagia split). This gives a weighting of [redacted] and corresponding threshold of [redacted] for the EAGs base-case from ECM3, and a weighting of [redacted] and corresponding threshold of [redacted] for the Companys base-case from ECM3.

Given the uncertainty in the evidence the committee requested the ICERs with 90% of the usual QALY weighting applied, these are presented in Table 3.

TABLE 3 WEIGHTED COST-EFFECTIVENESS RESULTS FOR THE EAG BASE-CASE FROM ECM3 AND THE COMPANY BASE-CASE FROM ECM3: PAEDIATRIC AND MIXED POPULATIONS (UPDATED WITH NEW PAS DISCOUNT)

	Incremental Costs	Incremental undiscounted QALYs	ICER	Weighted ICER	90% of QALY weighting applied to ICER
Paediatric Initiation					
EAG base-case at ECM3 and Companys updated base case after ECM3, (75:25 severe:moderate hyperphagia at baseline)	[redacted]	[redacted]	£170,638	[redacted]	[redacted]
Company base-case at ECM3 (84:16 severe:moderate hyperphagia at baseline)	[redacted]	[redacted]	£165,165	[redacted]	[redacted]
Mixed population (60% paediatric)					
EAG base-case at ECM3 (75:25 severe:moderate hyperphagia at baseline)	[redacted]	[redacted]	£174,904	[redacted]	[redacted]
Company base-case at ECM3 (84:16 severe:moderate hyperphagia at baseline)	[redacted]	[redacted]	£169,658	[redacted]	[redacted]