

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

**Setmelanotide for treating obesity caused by LEPR or POMC deficiency
[ID3764]**

The following documents are made available to the consultees and commentators:

1. [Response to consultee, commentator and public comments on the Evaluation Consultation Document \(ECD\)](#)
2. [Comments on the Evaluation Consultation Document \(ECD\) from Rhythm Pharmaceuticals](#)
 - [Company response](#)
 - [Company additional analyses](#)
3. [Evidence Review Group critique of company comments on the ECD](#)
4. [Evidence Review Group report addendum](#)

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

Highly Specialised Technology Evaluation

Setmelanotide for treating obesity caused by LEPR or POMC deficiency

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They also have the right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Rhythm Pharmaceuticals (company)	<p>Section 3.15 Long-term treatment effects</p> <p><i>“The committee noted that evidence from the extension study RM-493-022 suggested a plateau of weight loss. Compared with their weight when entering the extension study, people with LEPR deficiency had further weight loss of 2 kg (1%, standard deviation not reported) at 25 weeks. However, at 89 weeks, people with POMC deficiency had gained an average of 8 kg (9% of extension study baseline weight, standard deviation not reported). Also, people with POMC deficiency had a small increase in BMI at 37 weeks (exact results are academic in confidence and cannot be reported here) ... The ERG stated that these results suggested a possible waning of treatment effect but noted the small number of people included in the extension study analyses. The committee noted these uncertainties in the evidence (see section 3.8) and concluded that setmelanotide’s long-term treatment effect is uncertain.”</i></p> <p>Rhythm would like to:</p> <ul style="list-style-type: none"> • First challenge the ERG’s belief that weight gain at 89 weeks seen in the Long-term extension study <i>RM-493-022</i> included in the initial Evidence submission suggests a possible waning of treatment effect and the committee’s conclusion that setmelanotide’s long-term treatment effect is uncertain. • Submit novel data supporting the long-term efficacy of setmelanotide <p>1. Analysis of weight gain at 89 weeks</p> <p>In the general population, the average male increases in weight by approx. 5 kg per year between ages 12 and 18 and the average female by approx. 3 kg per year [1,2].</p>	<p>Thank you for your comments. At the second meeting, the committee considered the additional evidence from the RM-493-022 further data cut. It agreed that the company’s assumption of BMI maintenance after the trial period was uncertain but acceptable for decision making. See FED sections 3.16 and 3.22.</p>

- Interim analysis of the extension study RM-493-022, for a specific cohort of █ POMC patients (as submitted in original NICE submission), had a mean age of █ years (range █ to █ years) [3] meaning that many of these patients were still growing and so would be expected to gain weight over a period of 2-3 years
- Considering this, over the 89 weeks of the study, an increase in weight of 8 kg for POMC patients is aligned to weight gain observed in adolescents within the general population.

Likewise, the slight increase in BMI levels in POMC patients at 37 weeks is in line with that expected in the general population and thus not an appropriate indication of waning treatment effect:

- BMI levels naturally increase for all adolescents. Data from CDC shows that a girl at the 50th percentile at age 12 will have a BMI of 18. By age 15 the BMI will have increased to 20 (a natural increase of approximately 0.66 BMI points per year) [4].
- For adolescents at the 95th percentile the increase in BMI points between age 12 and 15 is even greater at approximately 1 BMI point per year for either girls or boys [4] [5].
- The slight increase in BMI levels seen in the *RM-493-022* trial at week 37 reflects what is observed for adolescents within the general population and can be considered BMI stabilisation, rather than BMI gain

The argument for treatment stabilisation is further supported by waist circumference data from the long-term extension trial 022: of the POMC/PCSK1 patients aged 12 and over who entered the long-term extension study, waist circumference was maintained at week 37 – at inclusion in the study average waist circumference was █ cm (SD █) and at 37 weeks was █ cm (SD █) [6]. Again, that this is a maintenance of waist circumference in a population which contains a significant percentage of growing adolescents.

2. Novel data supporting the long-term efficacy of setmelanotide

Since the publication of the ECD, further data from the long-term extension study have also become available. These data, based on the full POMC/PCSK1/LEPR (PPL) cohort from 022, show that the clinically beneficial effects of setmelanotide continue to be observed in patients with POMC, PCSK1, and LEPR biallelic deficiency with up to █ years of treatment. These data demonstrate the

	<p>persistence of setmelanotide treatment and support its long-term use in patients with POMC, PCSK1, and LEPR biallelic deficiency[7].</p> <ul style="list-style-type: none"> • After █ and █ months of treatment mean (SD) percent change in BMI was █% (█%; n=█) and █% (█%; n=█), respectively compared to index trial baseline. For patients <18 years old, the mean (SD) change in BMI Z score after █ and █ months was █ (█; n=█) and █ (█; n=█), respectively [5]. The results are pooled for POMC/PCSK1 and LEPR. • No new safety issues were observed during long-term treatment. Only one patient discontinued because of adverse events unrelated to treatment. <p>Further, individual patient data from the latest data cut on █ patients (█ of them with more than █ years on therapy) has demonstrated the consistent long-term effect of setmelanotide for up to █ years of therapy [8]</p> <ul style="list-style-type: none"> • The majority of adult patients showing an initial response to setmelanotide, continue to see either a reduction or maintenance of weight and BMI from week 52 up until their last visit, [8], with: <ul style="list-style-type: none"> ○ █ out of █ adult patients showing █ of BMI of █ points between week 52 and last visit ○ █ out of █ adult patients showing █ of BMI of █ points between week 52 and last visit ○ █ out of █ adult patients showing an █ of BMI of █ points between week 52 and last visit ○ █ █ out of █ adult patients showing an █ of BMI of █ points but for one, explained by lack of compliance (as per index study CSR) • Similarly, the majority of pediatric patients showing an initial response to setmelanotide, continue to see either a reduction or maintenance of weight and BMI from week 52 up until their last visit, [8], with: <ul style="list-style-type: none"> ○ █ out of █ pediatric patients showing █ of BMI of █ points between week 52 and last visit ○ █ out of █ pediatric patients showing █ of BMI of █ points between week 52 and last visit ○ █ out of █ pediatric patients showing an █ of BMI lower than the growth as calculated from CDC charts due to aging between week 52 and last visit ○ █ out of █ pediatric patients showing an █ of BMI of █ points between week 52 and last visit ○ █ █ patient showing an █ of BMI of █ points 	
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	<p>The evidence summarised above demonstrates a consistent long-term effect of setmelanotide with several patients continuing to lose weight beyond the initial 52 weeks loss and several also reaching and maintaining BMI below the obesity range for their age group (1 out of 4 adult patients and 1 out of 4 paediatric patients)</p> <p>Rhythm would also like to point out that in the <i>RM-493-012</i> and <i>RM-493-015</i> trials patients were not allowed to initiate a diet, and exercise program, or lifestyle modifications beyond those already in place at baseline. In <i>RM-493-022</i>, patients did not receive specific dietary counselling, except to ensure appropriate nutritional intake to maintain growth in paediatric patients. This is different from real life where reduction of hyperphagia will allow implementation of a strict diet, and reduction in BMI will facilitate the introduction of an exercise program. Thus, weight and BMI reduction and / or maintenance can be expected to be stronger in real life than in the aforementioned trials.</p> <p>In the longer term, the continuation of treatment effect of setmelanotide can be explained biologically. POMC/PCSK1 and LEPR deficiencies are both caused by genetic defects that prevent healthy signalling in the MC4R pathway. Setmelanotide restores the missing component of the MC4R pathway, turning hunger 'off' and enabling patients to regulate food intake in both the short-term and the long-term. There is no evidence or reason to believe that:</p> <ul style="list-style-type: none"> • Setmelanotide ability to cross the blood brain barrier and reach the MC4 receptor will diminish over time • Setmelanotide ability to bind the MC4 receptor will diminish over time • The number of MC4 receptors will diminish over time • The activity of the MC4 receptor will diminish over time <p>Testimony from the patient expert during the Committee meeting that setmelanotide quickly reduces hyperphagia and that this benefit did not change over time with weight loss, further supports the long-term treatment effect of setmelanotide.</p> <p>As a result, Rhythm believes that there is minimal uncertainty to maintenance of the benefits of setmelanotide and that a possible waning of treatment effect is extremely unlikely in regards of the data available.</p> <p>References: [1] Girls UK Growth Chart 2-18 years. Accessible: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years [2] Boys UK Growth Chart 2-18 years. Accessible: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years [3] Table 16 Patient characteristics on inclusion in Study RM-493-022. Original Submission [ID3764] Setmelanotide HST evidence submission 3.0</p>	
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	<p>[4] Girls Body mass index-for-age percentiles. National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Accessible https://www.cdc.gov/growthcharts/data/set1clinical/cj411024.pdf</p> <p>[5] Boys Body mass index-for-age percentiles. National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Accessible https://www.cdc.gov/growthcharts/data/set2clinical/cj41c073.pdf</p> <p>[6] Table 53 Change in waist circumference for POMC/PCSK1 patients (Study RM-493-022 baseline data. Original Submission [ID3764] Setmelanotide HST evidence submission 3.0</p> <p>[7] Data on file. Submitted to NICE. [ID3764] setmelanotide HST Abstract submitted to ENDO 2022, as yet not accepted</p> <p>[8] Data on file. Submitted to NICE [ID3764] setmelanotide HST Full PPL cohort</p>	
<p>Rhythm Pharmaceuticals (company)</p>	<p>Section 3.26 Utility values for hyperphagia</p> <p><i>“The committee considered that both the company’s and ERG’s utility multiplier values were likely to overestimate the detrimental impact of severe hyperphagia on quality of life...It was also concerned about the discrepancy on utility values applied for hyperphagia between the metreleptin appraisal and this topic, especially that for severe hyperphagia. The committee concluded that there was significant uncertainty in both company’s and ERG’s utility values for severe hyperphagia and this should be explored.”</i></p> <p>Based on all evidence available Rhythm would like to challenge the committee’s conclusion that there is significant uncertainty in the company’s utility values for severe hyperphagia:</p> <ol style="list-style-type: none"> 1. It is not appropriate to compare the ‘hyperphagia’ utility value from the metreleptin submission, which describes mild hyperphagia, with the ‘severe hyperphagia’ utility value obtained in the Vignette study. <ul style="list-style-type: none"> ○ The description of hyperphagia given to participants in the discrete choice experiment (DCE) from where metreleptin sourced their utility value, focussed on the symptoms of the disease e.g. long-term diabetes complications, faster organ damage progression, rather than the impact on health-related quality of life. ○ Where health-related quality of life did feature in the description this was limited to: impaired social function (ability to work/go to school) and depression and other mental health complications (e.g. anxiety) ○ This description aligns more to the ‘mild’ hyperphagia described in the Vignette study, as evidenced by the similarity between the DCE disutility value (0.11) and the ‘mild hyperphagia’ disutility value (■) obtained from the Vignette study. 2. The Vignette study was a rigorous study carried out in ■ members of the UK general 	<p>Thank you for your comments. In the second meeting, the committee considered the company’s response and alternative utility multipliers for severe hyperphagia. It acknowledged that, while severe hyperphagia is debilitating and all-consuming, the inclusion of negative values likely overestimated the quality-of-life decrement. So, it considered one of the company’s scenario which normalised the negative values from the vignette study to zero for decision making. See FED section 3.27.</p>

	<p>population using a time-trade-off (TTO) approach described in TSD11 'Alternatives to EQ-5D for generating health state utility values' [1] which clearly states that such approach should be conducted in the general population and not by patients 'The scoring should be based on UK general population values elicited using a choice-based technique' 'There are technical and ethical obstacles to collecting health state valuation data from patients that ask them life and death questions, such as TTO and SG. However, the main problem in the context of a NICE submission is that they are not the same as general population values.'</p> <p>3. The Vignette study is the only published data source for hyperphagia utility values and as such is the most credible evidence available on which to base utility values for mild, moderate and severe hyperphagia.</p> <ul style="list-style-type: none"> o The definition of the vignettes for mild, moderate and severe hyperphagia were based on symptoms detailed in the Second Consensus Conference on Hyperphagia [2] o These definitions were further validated through discussions with physicians experienced in treating patients with hyperphagia in the UK and in the US <p>4. Severe hyperphagia is a debilitating condition and this is reflected in the utility multiplier of ■ derived from the Vignette study. The lives of patients with severe hyperphagia are dominated by food to the point that it becomes all-consuming and there is little time for other activities. This is reflected in the description of the severe health state described in the Vignette study and validated by clinicians experienced in the treatment of POMC/PCSK1 and LEPR patients:</p> <p><i>In severe hyperphagia:</i></p> <ul style="list-style-type: none"> o Patients almost never feel full after a normally sized meal, o Thinking about food almost always interferes with activities of normal daily living, o Patients eat to the point of discomfort at most meals and eat almost constantly, o They wake up hungry and eat during the night o They become extremely distressed when denied food, o Because of hunger and eating behaviour they have severe problems performing daily activities and severe problems with relationships. <p>5. Of the ■ members of the UK general population who participated in the Vignette study, ■ respondents rated at least one negative utility value (indicating a health state perceived to be worse than dead) and ■ rated at least one utility of -1 (the lowest possible score). The following are quotes from participants who scored severe hyperphagia at -1, justifying why</p>	
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	<p>they gave this response:</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>6. These quotes highlight that the results of the Vignette study were based on a full understanding of what it meant to score the health state negatively.</p> <p>7. Rhythm has sought further expert advice on the impact of severe hyperphagia from [REDACTED], a specialist in Prader Willi Syndrome, another condition with a significant and severe hyperphagia element. He provided independent confirmation of the severity of 'severe hyperphagia' and the non-linear relationship between mild, moderate and severe health states [3].</p> <p>In conclusion, the utility value obtained for severe hyperphagia ([REDACTED]) in the Vignette study reflects the true impact of severe hyperphagia on patients' lives and its impact is exponential compared to mild hyperphagia. Evidence suggests it is appropriate for estimating the detrimental impact of severe hyperphagia on quality of life.</p> <p>Rhythm nevertheless acknowledges that alternative methods for analysing the results of the vignette study could be explored. Using a conservative alternative, accepted methodology, whereby derived utility values less than 0 were set to 0 [see Appendix] a utility multiplier of [REDACTED] is obtained for severe hyperphagia. A scenario analysis using this value can be found in the Appendix.</p>	
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	<p>[1] Brazier, J.E., Rowen, D. NICE DSU Technical Support Document 11: Alternatives to EQ-5D for generating health state utility values. 2011. Available from http://www.nicedsu.org.uk</p> <p>[2] Heymsfield, SB et al. Hyperphagia: Current Concepts and Future Directions Proceedings of the 2nd International Conference on Hyperphagia. Obesity (Silver Spring) 2014 Feb; 22 (0 1):S1-S17</p> <p>[3] Data on file. Statement from [REDACTED]</p>	
<p>Rhythm Pharmaceuticals (company)</p>	<p>Section 3.29 Criteria for applying a QALY weighting</p> <p><i>“The committee noted that some of the company and ERG’s analyses showed QALY gains within this range. However, it recalled the uncertainties surrounding the modelling, including the long-term treatment effect of setmelanotide and utility values for severe hyperphagia. The committee concluded that it is unclear if the criteria for applying a QALY weighting is met.”</i></p> <p>Rhythm acknowledges that uncertainties do exist in the modelling. However, the company believes that it has followed a very conservative approach to the development of the HEOR model and that resolving these uncertainties will only lead to reduced ICERs</p> <ol style="list-style-type: none"> 1. The case for the long-term treatment effect of setmelanotide and utility values for severe hyperphagia has been made in responses 1 and 2 above <ol style="list-style-type: none"> a. In addition, the long-term BMI regain scenarios provided in the Appendix show the relative insensitivity of the ICER to this parameter, even in scenarios which model more extreme weight gain scenarios that are not consistent with the available data. 2. The company did not integrate in the model several benefits that would lead to additional QALY generation but could not be quantified. Amongst those are: <ul style="list-style-type: none"> • Not including a caregiver or sibling disutility (as pointed by ERG) • Not including several of the comorbidities associated to children or adolescent obesity such as (but not limited to): <ul style="list-style-type: none"> ○ Increased risk of stroke in adolescents with increased BMI [4] ○ Increased risk of asthma exacerbation due to impaired lung development [5] ○ Increased risk of polycystic ovary syndrome [6] 	<p>Thank you for your comments. At the second meeting, the committee acknowledged there was some uncertainty in the cost effectiveness estimates but that the extra health and quality-of-life benefits of setmelanotide are likely to be substantial. It agreed that the criteria for applying a QALY weighting was met. See FED section 3.31.</p>

	<ul style="list-style-type: none"> ○ Increased risk to physical health due to poor motor coordination [7] • Estimating the impact of comorbidities such as T2DM and cardiovascular comorbidities using general population estimates, when the impact in POMC/PCSK1 and LEPR patients is likely to be greater given the early onset of obesity in these conditions • Not including any additional costs for acute events and emergency admissions due to the over-eating resulting from hyperphagia [8,9] <p>3. Best Supportive Care is defined simply by diet and exercise in general obesity but does not include additional costs to support patients with severe hyperphagia and their caregivers</p> <p>4. In addition, modelling shows that Lifetime QALYs are higher for paediatric patients [see modelling in Appendix]. We expect that moving forward novel POMC/PCSK1 and LEPR patients will be diagnosed early in life as genetic testing for monogenic obesity (including POMC and LEPR) is included in the NHS National Genomic test Directory. In line with the key priorities of the Rare Disease Framework, newly diagnosed patients would therefore potentially be able to start treatment with setmelanotide as early as from age 6, according to the licenced indication, and therefore able to accrue the health and quality of life benefits of treatment over the full course of their lifetime</p> <p>5. Finally, the company did not model the impact of the disease on school/work and social lives of patients, which can be very negative, as detailed by the patient representative during the NICE committee meeting.</p> <p>In summary, by not applying a QALY weighting, the company believes the true impact of setmelanotide on the lives' of patients with POMC/PCSK1 or LEPR deficiency would be significantly under-estimated. The majority of patients become obese as early as 2 years of age and in LEPR patients in particular there are a proportion who die in childhood as a result of respiratory tract infections caused by an interaction between obesity and the mild immunosuppressive nature of LEPR deficiency [3]. It is therefore very plausible that by preventing or reversing such extreme obesity and hyperphagia, setmelanotide provides patients with considerable QALY gains over their lifetime. Rhythm have gone to significant effort to reduce uncertainties through commissioning a large, robust, UK based study to determine utility values and through the continued collection of long-term data. The modelling of setmelanotide's cost-effectiveness has been conservative and the true ICER is likely to be lower than those presented. Based on this, it would not be credible to suggest the criteria for applying a QALY has not been met.</p> <p>We request the committee to reconsider the evidence and value that setmelanotide brings to UK POMC/PCSK1 and LEPR patients.</p>	
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	<p>[1] Personal communication with [REDACTED]</p> <p>[2] Djalalinia S, Qorbani M, Peykari N, Kelishadi R. Health impacts of obesity. <i>Pakistan journal of medical sciences</i>. 2015;31(1):239.</p> <p>[3] Personal communication with [REDACTED]</p> <p>[4] Aya Bardugo et al. Body Mass Index in 1.9 Million Adolescents and Stroke in Young Adulthood. <i>Stroke</i>. 2021;52:2043–2052</p> <p>[5] Hochart A et al. Dramatic impact of morbid obesity on child lung development. <i>Archives de Pédiatrie</i> 28 (2021): 186-190</p> <p>[6] Barber TM and Franks S, Obesity and polycystic ovary syndrome. <i>Clinical Endocrinology</i>. 2021;95:531–541.</p> <p>[7] Barros WMA, Silva KG, Silva RKP, Souza APS, Silva ABJ, Silva MRM, Fernandes MSS, Souza SL and Souza VON (2022) Effects of Overweight/Obesity on Motor Performance in Children: A Systematic Review. <i>Front. Endocrinol.</i> 12:759165. doi: 10.3389/fendo.2021.759165</p> <p>[8] Personal communication with [REDACTED]</p> <p>[9] Bellis S, Kuhn I, Adams S, Mullarkey L, Holland A. The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality. <i>European Journal of Medical Genetics</i> 65 (2022) 104379</p>	
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Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None		

Comments received from commentators

Commentator	Comment	Response
None		

Confidential until publication

Comments received from members of the public

Role*	Section	Comment	Response
None			

Summary of comments received from members of the public

Theme	Response
None	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 21 February 2022. Please submit via NICE Docs.

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> • 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? <p>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:</p> <ul style="list-style-type: none"> • 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. <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Rhythm Pharmaceuticals</p>
<p>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>We, Rhythm Pharmaceuticals do not have past or current, direct or indirect links to, or funding from, the tobacco industry</p>
<p>Name of commentator person completing form:</p>	<p>Nicolas Touchot</p>
<p>Comment number</p>	<p style="text-align: center;">Comments</p> <p style="text-align: center;">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.</p>

Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 21 February 2022. Please submit via NICE Docs.

1	<p>Section 3.15 Long-term treatment effects</p> <p><i>“The committee noted that evidence from the extension study RM-493-022 suggested a plateau of weight loss. Compared with their weight when entering the extension study, people with LEPR deficiency had further weight loss of 2 kg (1%, standard deviation not reported) at 25 weeks. However, at 89 weeks, people with POMC deficiency had gained an average of 8 kg (9% of extension study baseline weight, standard deviation not reported). Also, people with POMC deficiency had a small increase in BMI at 37 weeks (exact results are academic in confidence and cannot be reported here) ... The ERG stated that these results suggested a possible waning of treatment effect but noted the small number of people included in the extension study analyses. The committee noted these uncertainties in the evidence (see section 3.8) and concluded that setmelanotide’s long-term treatment effect is uncertain.”</i></p> <p>Rhythm would like to:</p> <ul style="list-style-type: none"> • First challenge the ERG’s belief that weight gain at 89 weeks seen in the Long-term extension study <i>RM-493-022</i> included in the initial Evidence submission suggests a possible waning of treatment effect and the committee’s conclusion that setmelanotide’s long-term treatment effect is uncertain. • Submit novel data supporting the long-term efficacy of setmelanotide <p>1. Analysis of weight gain at 89 weeks</p> <p>In the general population, the average male increases in weight by approx. 5 kg per year between ages 12 and 18 and the average female by approx. 3 kg per year [1,2].</p> <ul style="list-style-type: none"> • Interim analysis of the extension study <i>RM-493-022</i>, for a specific cohort of ‘academic / commercial in confidence information removed’ POMC patients (as submitted in original NICE submission), had a mean age of ‘academic / commercial in confidence information removed’ years (range ‘academic / commercial in confidence information removed’ years) [3] meaning that many of these patients were still growing and so would be expected to gain weight over a period of 2-3 years • Considering this, over the 89 weeks of the study, an increase in weight of 8 kg for POMC patients is aligned to weight gain observed in adolescents within the general population. <p>Likewise, the slight increase in BMI levels in POMC patients at 37 weeks is in line with that expected in the general population and thus not an appropriate indication of waning treatment effect:</p> <ul style="list-style-type: none"> • BMI levels naturally increase for all adolescents. Data from CDC shows that a girl at the 50th percentile at age 12 will have a BMI of 18. By age 15 the BMI will have increased to 20 (a natural increase of approximately 0.66 BMI points per year) [4]. • For adolescents at the 95th percentile the increase in BMI points between age 12 and 15 is even greater at approximately 1 BMI point per year for either girls or boys [4] [5]. • The slight increase in BMI levels seen in the <i>RM-493-022</i> trial at week 37 reflects what is observed for adolescents within the general population and can be considered BMI stabilisation, rather than BMI gain <p>The argument for treatment stabilisation is further supported by waist circumference data from the long-term extension trial 022: of the POMC/PCSK1 patients aged 12 and over who entered the</p>
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Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

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	<p>long-term extension study, waist circumference was maintained at week 37 – at inclusion in the study average waist circumference was ‘academic / commercial in confidence information removed’ and at 37 weeks was ‘academic / commercial in confidence information removed’ [6]. Again, that this is a maintenance of waist circumference in a population which contains a significant percentage of growing adolescents.</p> <p>2. Novel data supporting the long-term efficacy of setmelanotide</p> <p>Since the publication of the ECD, further data from the long-term extension study have also become available. These data, based on the full POMC/PCSK1/LEPR (PPL) cohort from 022, show that the clinically beneficial effects of setmelanotide continue to be observed in patients with POMC, PCSK1, and LEPR biallelic deficiency with up to ‘academic / commercial in confidence information removed’ years of treatment. These data demonstrate the persistence of setmelanotide treatment and support its long-term use in patients with POMC, PCSK1, and LEPR biallelic deficiency[7].</p> <ul style="list-style-type: none"> • After ‘academic / commercial in confidence information removed’ months of treatment mean (SD) percent change in BMI was ‘academic / commercial in confidence information removed’ and ‘academic / commercial in confidence information removed’, respectively compared to index trial baseline. For patients <18 years old, the mean (SD) change in BMI Z score after ‘academic / commercial in confidence information removed’ months was ‘academic / commercial in confidence information removed’ and ‘academic / commercial in confidence information removed’, respectively [5]. The results are pooled for POMC/PCSK1 and LEPR. • No new safety issues were observed during long-term treatment. Only one patient discontinued because of adverse events unrelated to treatment. <p>Further, individual patient data from the latest data cut on ‘academic / commercial in confidence information removed’ patients (‘academic / commercial in confidence information removed’ of them with more than ‘academic / commercial in confidence information removed’ years on therapy) has demonstrated the consistent long-term effect of setmelanotide for up to ‘academic / commercial in confidence information removed’ years of therapy [8]</p> <ul style="list-style-type: none"> • The majority of adult patients showing an initial response to setmelanotide, continue to see either a reduction or maintenance of weight and BMI from week 52 up until their last visit, [8], with: <ul style="list-style-type: none"> ○ ‘academic / commercial in confidence information removed’ adult patients showing ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit ○ ‘academic / commercial in confidence information removed’ adult patients showing ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit ○ ‘academic / commercial in confidence information remove’ adult patients showing an ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit ○ ‘academic / commercial in confidence information removed’ adult patients showing an ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points but for one, explained by lack of compliance (as per index study CSR)
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- Similarly, the majority of pediatric patients showing an initial response to setmelanotide, continue to see either a reduction or maintenance of weight and BMI from week 52 up until their last visit, [8], with:
 - ‘academic / commercial in confidence information removed’ pediatric patients showing ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit
 - ‘academic / commercial in confidence information removed’ pediatric patients showing ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit
 - ‘academic / commercial in confidence information removed’ pediatric patients showing an ‘academic / commercial in confidence information removed’ of BMI lower than the growth as calculated from CDC charts due to aging between week 52 and last visit
 - ‘academic / commercial in confidence information removed’ pediatric patients showing an ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points between week 52 and last visit
 - ‘academic / commercial in confidence information removed’ patient showing an ‘academic / commercial in confidence information removed’ of BMI of ‘academic / commercial in confidence information removed’ points

The evidence summarised above demonstrates a consistent long-term effect of setmelanotide with several patients continuing to lose weight beyond the initial 52 weeks loss and several also reaching and maintaining BMI below the obesity range for their age group (‘academic / commercial in confidence information removed’ adult patients and ‘academic / commercial in confidence information removed’ paediatric patients)

Rhythm would also like to point out that in the *RM-493-012* and *RM-493-015* trials patients were not allowed to initiate a diet, and exercise program, or lifestyle modifications beyond those already in place at baseline. In *RM-493-022*, patients did not receive specific dietary counselling, except to ensure appropriate nutritional intake to maintain growth in paediatric patients. This is different from real life where reduction of hyperphagia will allow implementation of a strict diet, and reduction in BMI will facilitate the introduction of an exercise program. Thus, weight and BMI reduction and / or maintenance can be expected to be stronger in real life than in the aforementioned trials.

In the longer term, the continuation of treatment effect of setmelanotide can be explained biologically. POMC/PCSK1 and LEPR deficiencies are both caused by genetic defects that prevent healthy signalling in the MC4R pathway. Setmelanotide restores the missing component of the MC4R pathway, turning hunger ‘off’ and enabling patients to regulate food intake in both the short-term and the long-term. There is no evidence or reason to believe that:

- Setmelanotide ability to cross the blood brain barrier and reach the MC4 receptor will diminish over time
- Setmelanotide ability to bind the MC4 receptor will diminish over time
- The number of MC4 receptors will diminish over time
- The activity of the MC4 receptor will diminish over time

Testimony from the patient expert during the Committee meeting that setmelanotide quickly reduces hyperphagia and that this benefit did not change over time with weight loss, further supports the long-term treatment effect of setmelanotide.

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	<p>As a result, Rhythm believes that there is minimal uncertainty to maintenance of the benefits of setmelanotide and that a possible waning of treatment effect is extremely unlikely in regards of the data available.</p> <p>References: [1] Girls UK Growth Chart 2-18 years. Accessible: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years [2] Boys UK Growth Chart 2-18 years. Accessible: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years [3] Table 16 Patient characteristics on inclusion in Study RM-493-022. Original Submission [ID3764] Setmelanotide HST evidence submission 3.0 [4] Girls Body mass index-for-age percentiles. National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Accessible https://www.cdc.gov/growthcharts/data/set1clinical/cj41i024.pdf [5] Boys Body mass index-for-age percentiles. National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Accessible https://www.cdc.gov/growthcharts/data/set2clinical/cj41c073.pdf [6] Table 53 Change in waist circumference for POMC/PCSK1 patients (Study RM-493-022 baseline data. Original Submission [ID3764] Setmelanotide HST evidence submission 3.0 [7] Data on file. Submitted to NICE. [ID3764] setmelanotide HST Abstract submitted to ENDO 2022, as yet not accepted [8] Data on file. Submitted to NICE [ID3764] setmelanotide HST Full PPL cohort</p>
2	<p>Section 3.26 Utility values for hyperphagia</p> <p><i>“The committee considered that both the company’s and ERG’s utility multiplier values were likely to overestimate the detrimental impact of severe hyperphagia on quality of life...It was also concerned about the discrepancy on utility values applied for hyperphagia between the metreleptin appraisal and this topic, especially that for severe hyperphagia. The committee concluded that there was significant uncertainty in both company’s and ERG’s utility values for severe hyperphagia and this should be explored.”</i></p> <p>Based on all evidence available Rhythm would like to challenge the committee’s conclusion that there is significant uncertainty in the company’s utility values for severe hyperphagia:</p> <ol style="list-style-type: none"> 1. It is not appropriate to compare the ‘hyperphagia’ utility value from the metreleptin submission, which describes mild hyperphagia, with the ‘severe hyperphagia’ utility value obtained in the Vignette study. <ul style="list-style-type: none"> ○ The description of hyperphagia given to participants in the discrete choice experiment (DCE) from where metreleptin sourced their utility value, focussed on the symptoms of the disease e.g. long-term diabetes complications, faster organ damage progression, rather than the impact on health-related quality of life. ○ Where health-related quality of life did feature in the description this was limited to: impaired social function (ability to work/go to school) and depression and other mental health complications (e.g. anxiety) ○ This description aligns more to the ‘mild’ hyperphagia described in the Vignette study, as evidenced by the similarity between the DCE disutility value (0.11) and the ‘mild hyperphagia’ disutility value (‘academic / commercial in confidence information removed’) obtained from the Vignette study. 2. The Vignette study was a rigorous study carried out in ‘academic / commercial in confidence information removed’ members of the UK general population using a time-trade-off (TTO) approach described in TSD11 ‘Alternatives to EQ-5D for generating health

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	<p>state utility values' [1] which clearly states that such approach should be conducted in the general population and not by patients '<i>The scoring should be based on UK general population values elicited using a choice-based technique</i>' '<i>There are technical and ethical obstacles to collecting health state valuation data from patients that ask them life and death questions, such as TTO and SG. However, the main problem in the context of a NICE submission is that they are not the same as general population values.</i>'</p> <p>3. The Vignette study is the only published data source for hyperphagia utility values and as such is the most credible evidence available on which to base utility values for mild, moderate and severe hyperphagia.</p> <ul style="list-style-type: none">○ The definition of the vignettes for mild, moderate and severe hyperphagia were based on symptoms detailed in the Second Consensus Conference on Hyperphagia [2]○ These definitions were further validated through discussions with physicians experienced in treating patients with hyperphagia in the UK and in the US <p>4. Severe hyperphagia is a debilitating condition and this is reflected in the utility multiplier of 'academic / commercial in confidence information removed' derived from the Vignette study. The lives of patients with severe hyperphagia are dominated by food to the point that it becomes all-consuming and there is little time for other activities. This is reflected in the description of the severe health state described in the Vignette study and validated by clinicians experienced in the treatment of POMC/PCSK1 and LEPR patients:</p> <p><i>In severe hyperphagia:</i></p> <ul style="list-style-type: none">○ Patients almost never feel full after a normally sized meal,○ Thinking about food almost always interferes with activities of normal daily living,○ Patients eat to the point of discomfort at most meals and eat almost constantly,○ They wake up hungry and eat during the night○ They become extremely distressed when denied food,○ Because of hunger and eating behaviour they have severe problems performing daily activities and severe problems with relationships. <p>5. Of the 'academic / commercial in confidence information removed' members of the UK general population who participated in the Vignette study, 'academic / commercial in confidence information removed' respondents rated at least one negative utility value (indicating a health state perceived to be worse than dead) and 'academic / commercial in confidence information removed' rated at least one utility of -1 (the lowest possible score). The following are quotes from participants who scored severe hyperphagia at -1, justifying why they gave this response:</p> <p>'academic / commercial in confidence information removed'</p> <p>'academic / commercial in confidence information removed'</p> <p>'academic / commercial in confidence information removed'</p> <p>'academic / commercial in confidence information removed'</p>
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	<p>6. These quotes highlight that the results of the Vignette study were based on a full understanding of what it meant to score the health state negatively.</p> <p>7. Rhythm has sought further expert advice on the impact of severe hyperphagia from ‘academic / commercial in confidence information removed’, a specialist in Prader Willi Syndrome, another condition with a significant and severe hyperphagia element. He provided independent confirmation of the severity of ‘severe hyperphagia’ and the non-linear relationship between mild, moderate and severe health states [3].</p> <p>In conclusion, the utility value obtained for severe hyperphagia (‘academic / commercial in confidence information removed’) in the Vignette study reflects the true impact of severe hyperphagia on patients’ lives and its impact is exponential compared to mild hyperphagia. Evidence suggests it is appropriate for estimating the detrimental impact of severe hyperphagia on quality of life.</p> <p>Rhythm nevertheless acknowledges that alternative methods for analysing the results of the vignette study could be explored. Using a conservative alternative, accepted methodology, whereby derived utility values less than 0 were set to 0 [see Appendix] a utility multiplier of ‘academic / commercial in confidence information removed’ is obtained for severe hyperphagia. A scenario analysis using this value can be found in the Appendix.</p> <p>[1] Brazier, J.E., Rowen, D. NICE DSU Technical Support Document 11: Alternatives to EQ-5D for generating health state utility values. 2011. Available from http://www.nicedsu.org.uk [2] Heymsfield, SB et al. Hyperphagia: Current Concepts and Future Directions Proceedings of the 2nd International Conference on Hyperphagia. Obesity (Silver Spring) 2014 Feb; 22 (0 1):S1-S17 [3] Data on file. Statement from ‘academic / commercial in confidence information removed’</p>
(3)	<p>Section 3.29 Criteria for applying a QALY weighting</p> <p><i>“The committee noted that some of the company and ERG’s analyses showed QALY gains within this range. However, it recalled the uncertainties surrounding the modelling, including the long-term treatment effect of setmelanotide and utility values for severe hyperphagia. The committee concluded that it is unclear if the criteria for applying a QALY weighting is met.”</i></p> <p>Rhythm acknowledges that uncertainties do exist in the modelling. However, the company believes that it has followed a very conservative approach to the development of the HEOR model and that resolving these uncertainties will only lead to reduced ICERs</p> <ol style="list-style-type: none"> 1. The case for the long-term treatment effect of setmelanotide and utility values for severe hyperphagia has been made in responses 1 and 2 above <ol style="list-style-type: none"> a. In addition, the long-term BMI regain scenarios provided in the Appendix show the relative insensitivity of the ICER to this parameter, even in scenarios which model more extreme weight gain scenarios that are not consistent with the available data. 2. The company did not integrate in the model several benefits that would lead to additional QALY generation but could not be quantified. Amongst those are:

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- Not including a caregiver or sibling disutility (as pointed by ERG)
 - Not including several of the comorbidities associated to children or adolescent obesity such as (but not limited to):
 - Increased risk of stroke in adolescents with increased BMI [4]
 - Increased risk of asthma exacerbation due to impaired lung development [5]
 - Increased risk of polycystic ovary syndrome [6]
 - Increased risk to physical health due to poor motor coordination [7]
 - Estimating the impact of comorbidities such as T2DM and cardiovascular comorbidities using general population estimates, when the impact in POMC/PCSK1 and LEPR patients is likely to be greater given the early onset of obesity in these conditions
 - Not including any additional costs for acute events and emergency admissions due to the over-eating resulting from hyperphagia [8,9]
3. Best Supportive Care is defined simply by diet and exercise in general obesity but does not include additional costs to support patients with severe hyperphagia and their caregivers
 4. In addition, modelling shows that Lifetime QALYs are higher for paediatric patients [see modelling in Appendix]. We expect that moving forward novel POMC/PCSK1 and LEPR patients will be diagnosed early in life as genetic testing for monogenic obesity (including POMC and LEPR) is included in the NHS National Genomic test Directory. In line with the key priorities of the Rare Disease Framework, newly diagnosed patients would therefore potentially be able to start treatment with setmelanotide as early as from age 6, according to the licenced indication, and therefore able to accrue the health and quality of life benefits of treatment over the full course of their lifetime
 5. Finally, the company did not model the impact of the disease on school/work and social lives of patients, which can be very negative, as detailed by the patient representative during the NICE committee meeting.

In summary, by not applying a QALY weighting, the company believes the true impact of setmelanotide on the lives' of patients with POMC/PCSK1 or LEPR deficiency would be significantly under-estimated. The majority of patients become obese as early as 2 years of age and in LEPR patients in particular there are a proportion who die in childhood as a result of respiratory tract infections caused by an interaction between obesity and the mild immunosuppressive nature of LEPR deficiency [3]. It is therefore very plausible that by preventing or reversing such extreme obesity and hyperphagia, setmelanotide provides patients with considerable QALY gains over their lifetime. Rhythm have gone to significant effort to reduce uncertainties through commissioning a large, robust, UK based study to determine utility values and through the continued collection of long-term data. The modelling of setmelanotide's cost-effectiveness has been conservative and the true ICER is likely to be lower than those presented. Based on this, it would not be credible to suggest the criteria for applying a QALY has not been met.

We request the committee to reconsider the evidence and value that setmelanotide brings to UK POMC/PCSK1 and LEPR patients.

[1] Personal communication with 'academic / commercial in confidence information removed'

[2] Djalalinia S, Qorbani M, Peykari N, Kelishadi R. Health impacts of obesity. Pakistan journal of medical sciences. 2015;31(1):239.

[3] Personal communication with 'academic / commercial in confidence information removed'

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	<p>[4] Aya Bardugo et al. Body Mass Index in 1.9 Million Adolescents and Stroke in Young Adulthood. <i>Stroke</i>. 2021;52:2043–2052</p> <p>[5] Hochart A et al. Dramatic impact of morbid obesity on child lung development. <i>Archives de Pédiatrie</i> 28 (2021): 186-190</p> <p>[6] Barber TM and Franks S, Obesity and polycystic ovary syndrome. <i>Clinical Endocrinology</i>. 2021;95:531–541.</p> <p>[7] Barros WMA, Silva KG, Silva RKP, Souza APS, Silva ABJ, Silva MRM, Fernandes MSS, Souza SL and Souza VON (2022) Effects of Overweight/Obesity on Motor Performance in Children: A Systematic Review. <i>Front. Endocrinol.</i> 12:759165. doi: 10.3389/fendo.2021.759165</p> <p>[8] Personal communication with 'academic / commercial in confidence information removed'</p> <p>[9] Bellis S, Kuhn I, Adams S, Mullarkey L, Holland A. The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality. <i>European Journal of Medical Genetics</i> 65 (2022) 104379</p>

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- 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.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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 appraisal consultation document, please submit these separately.

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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.

Table 1: Revised base case results at NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	0.10				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	316,635

Table 2: Revised base case results including revised PAS discount of 'academic/commercial in confidence data removed'

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	12.21	0.08				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	212,244

As per the Committee's request, the following scenarios were also explored:

1. Paediatric patients only

In this scenario all patients are assumed to start treatment with setmelanotide as paediatrics. Average age of initiation is 7 years. As described above, Rhythm believes that this scenario is likely to be closer to the future UK situation where the vast majority of patients are diagnosed in early childhood and therefore able to start treatment with setmelanotide as children.

Incremental undiscounted QALYs: ██████

Table 3: Paediatric patients only NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	33,210	23.78	0.18				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	298,711

Table 4: Paediatric patients only PAS price ██████ discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	33,210	20.68	0.13				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	200,079

2. Alternative utility values for severe hyperphagia

In this scenario, any negative utility scores from responders for any of the health states were set to zero. As expected, there was no change to the TTO results from health states A and B, a slight change to health state C, and a possibly meaningful change to health state D although notably, the

scores remain very low. Please refer to the table below for comparison of the published TTO results with the revised results.

Health State	Original means with negative numbers	Revised means with all negative numbers changed to zero
A: No Hyperphagia	■	■
B: Mild Hyperphagia	■	■
C: Moderate Hyperphagia	■	■
D: Severe Hyperphagia	■	■

Incremental undiscounted QALYs: ■

Table 5: Alternative utility multiplier for severe hyperphagia at NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	1.93				
Setmelanotide + BSC	■	■	■	■	■	■	356,793

Table 6: Alternative utility multiplier for severe hyperphagia at PAS price 33% discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	12.21	1.35				
Setmelanotide + BSC	■	■	■	■	■	■	239,163

3. Using 1.5% discount rate for health effects and costs

Discounting outcomes at 3.5% greatly undervalues the positive QALY impact of setmelanotide treatment later in life. Given we believe the uncertainty over the long-term treatment effect of setmelanotide and utility values for severe hyperphagia have been addressed, a scenario with a 1.5% discount rate is presented.

Incremental undiscounted QALYs: ■

Table 7: 1.5% discount rate for health effects and costs at NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	40,313	19.02	0.10				
Setmelanotide + BSC	■	■	■	■	■	■	315,264

Table 8: 1.5% discount rate for health effects and costs at PAS price ■ discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	40,313	14.36	0.09				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	211,481

4. Exploring setmelanotide’s long-term treatment effect on BMI

In order to explore the model’s sensitivity to long-term treatment effect on BMI, a number of scenarios were investigated:

- Scenario a: 20% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial
- Scenario b: 50% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial
- Scenario c: After the trial all patients lose 1 BMI level over their lifetime

These scenarios show that despite the uncertainty in long-term BMI regain or maintenance beyond three years, even the most aggressive BMI regain scenarios do not increase the ICER substantially and have a very small impact on the incremental QALYs.

Due to the relative insensitivity of the model to weight regain scenarios, as determined in the original DSA and scenario analyses, the implementation of weight regain had not been previously scrutinised. In more recent implementation and consideration of weight regain scenarios, it was found that the patient cohort in the model could follow a rather unrealistic weight regain trajectory that permitted treated subjects to achieve higher BMI than they had before treatment. As a consequence, a parameter was added to the model to permit weight regain to be “capped” after a user-specified length of time.

Scenario 4a

Incremental undiscounted QALYs: ██████████

Table 9: 20% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial. NHS List price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	0.10				
Setmelanotide	████████	██████	██████	████████	██████	██████	320,507

Table 10: 20% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial. PAS price ██████ discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	12.21	0.08				
Setmelanotide + BSC	████████	██████	██████	████████	██████	██████	214,898

Scenario 4b

Incremental undiscounted QALYs: [REDACTED]

Table 11: 50% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial. NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	0.10				
Setmelanotide	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	326,502

Table 12: 50% of LEPR patients regain 1 BMI level every 4 years capped at 10 years. POMC patients maintain their weight from end of trial. PAS price [REDACTED] discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	12.21	0.08				
Setmelanotide + BSC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	219,007

Scenario 4c

Incremental undiscounted QALYs: [REDACTED]

Table 13: After the trial all patients lose 1 BMI level over their lifetime. NHS list price

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	0.10				
Setmelanotide	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	315,535

Table 14: After the trial all patients lose 1 BMI level over their lifetime. PAS price [REDACTED] discount

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
BSC	31,748	19.02	0.10				
Setmelanotide + BSC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	211,508

References:

[1] Data on file

[2] UK Rare Disease Framework. Accessible at <https://www.gov.uk/government/publications/uk-rare-diseases-framework>

[2] Data on file provided to NICE: [ID3764] Setmelanotide DOF Full PPL cohort

Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

A Highly Specialised Technology Appraisal

Addendum #5

ERG Review of Company's Response to ECD and additional analyses including updated patient access scheme discount

31 March 2022

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1. INTRODUCTION

The purpose of this addendum is to provide NICE with additional information following a recently updated patient access scheme (PAS) discount for setmelanotide.

The Evidence Review Group (ERG) was requested to update the company revised base case, model results based on committee preference and model results for scenarios (Addendum 4 to the ERG report; Tables 3, 4 and 5, respectively) using the new PAS discount, though the ERG note that this discount was already included in the model used to generate these tables. NICE also requested that incremental cost-effectiveness ratios (ICERs) for subgroups by genetic type (proopiomelanocortin vs. leptin receptor deficiency) and population (adult vs. paediatric), using committee preferences and the new PAS discount, be provided.

Furthermore, the ERG was requested to provide the cumulative impact of each change made to the company's original base case that resulted in the ERG's preferred base case, again including the new PAS discount.

2. ERG RESPONSE

2.1. Changes to the company's model following ECD1

To address uncertainty raised by the committee in the evaluation committee decision 1 (ECD1), the company provided a revised base case analysis for consideration. The complete list of assumptions used, and the subsequent ERG critique thereof, are summarised in Table 1 below.

Note! This is a replication of Table 1 in Addendum 4 of the ERG report, included here for ease of reference and the sake of completeness.

Table 1: Company preferred assumptions in response to ECD1, and ERG critique thereof, vs committee, company and ERG preferred assumptions following EC1

Preferred assumptions following EC1			Company preferred assumptions and ERG critique following ECD1	
Committee preferred assumptions	Company preferred assumptions	ERG preferred assumptions	Company preferred assumptions	ERG comments
1. Population: overall population (LEPR, POMC, children and adults combined)	✓	✗	✓ (Company preferred a slightly different split)	The ERG did not regard that this was unreasonable based on the data provided.
2. Hyperphagia: treatment effect applied as a half-cycle correction in the first cycle	✗ (start of first cycle)	✗ (end of first cycle)	✗ (end of first cycle)	The ERG preferred the committee's assumption in this instance given the underlying clinical rationale.
3. Separate doses for adults and children and by deficiency	✗	✓	✓	This is reflective of the committee's preference.
4. Mortality rate non-responders & BSC: Life expectancy converted to equivalent HR multiplier	✗	✓	✓	This is reflective of the committee's preference.
5. 1% discontinuation rate through lifetime	✗	✓	✓ (applied from 12 weeks onward)	The ERG considered that this change was in line with committee preference.
6. Utility multipliers for hyperphagia using the following values:				
a. Mild and moderate hyperphagia: vignette study values	✓	✓	✓	This is reflective of the committee's preference.
b. Severe hyperphagia: -0.33 accepting uncertainty remained	✗	✓	✗	This is not reflective of the committee's preference.

Preferred assumptions following EC1			Company preferred assumptions and ERG critique following ECD1	
7. Discount rate of 3.5% for both health benefits and costs	x	✓	✓	This change is reflective of the committee's preference.
New issues raised by the company				
8. Inclusion of carer disutilities	x	x	✓	The ERG regarded that this was inappropriate and better considered as a scenario analysis.
9. Long-term assumption of weight loss for POMC	x	x	✓	The ERG agreed that the provided data supported this change.
10. 100% of patients have severe hyperphagia	x	x	✓	The ERG agreed that this was broadly reflective of UK clinical practice

Abbreviations: BSC, best supportive care; EC1, evaluation consultation 1; ECD1, evaluation committee decision 1; ERG, Evidence Review Group; HR, hazard ratio; LEPR, leptin receptor; POMC, proopiomelanocortin

2.2. Company's revised base case and model changes

Note! The ERG noted that the new PAS discount had already been applied to the company revised base case, updated model results based on committee preference and updated model results for scenarios in Addendum 4 to the ERG report. However, for the sake of completeness in this section, the ERG has reproduced results included as Section 2.2.3, 2.2.4 and 2.2.5 in Addendum 4.

2.2.1. Company's revised base case

The revised base results using company's model based on the assumptions outlined in Section 2.2.3 of Addendum 4 to the ERG report; these results are reproduced in Table 2. Please note that the new PAS discount was already included in Addendum 4, therefore values in this table are identical to those presented in Addendum 4, Table 3.

Based on company's model, setmelanotide plus best supportive care (BSC) resulted in an undiscounted and discounted QALY gain of [REDACTED] and [REDACTED] respectively compared to BSC alone. The corresponding incremental costs (discounted) were [REDACTED] and the ICER (using discounted QALY gain) was £212,746. Based on the probabilistic analysis, the undiscounted and discounted QALY gain were similar at [REDACTED] and [REDACTED] respectively and the corresponding incremental costs was [REDACTED] with the incremental cost-effectiveness ratio (ICER) (using discounted QALY gain) of £215,454.

Table 2: Company revised base case results (with PAS)

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained
<i>Company revised base case results (deterministic)</i>							
Setmelanotide + BSC	████████	██	██	████████	██	██	£212,746
BSC	£29,882	0.07	0.09	-	-		-
<i>Company revised base case results (probabilistic)</i>							
Setmelanotide + BSC	████████	██	██	████████	██	██	£215,454
BSC	£29,826	0.09	0.12	-	-		-

Abbreviations: BSC, best supportive care; PAS, patient access scheme; QALYs, quality-adjusted life years

2.2.2. ERG preferred base case

This section reproduces the results of the ERG preferred base case which incorporated the committee preferences including PAS arrangements for setmelanotide, for both discounted and undiscounted quality-adjusted life year (QALY) gains, as reported in Section 2.2.4 of Addendum 4 to the ERG report. These values are reproduced in Table 3. **Note!** The new PAS discount was already included in Addendum 4, therefore values in this table are identical to those presented in Addendum 4, Table 4.

The ERG noted that there is a discrepancy between the results using the company's model versus the ERG version of the model (difference in ICER of around £2 to 3k), however, due to time constraints it was not possible to attribute this difference to a specific reason. Nevertheless, the ERG observed that the results were broadly comparable between the different versions of the model.

Setmelanotide plus best supportive care (BSC) resulted in an undiscounted and discounted QALY gain of [REDACTED] and [REDACTED] respectively compared to BSC alone. The corresponding incremental costs (discounted) were [REDACTED] and the ICER (using discounted QALY gain) was £324,925. Based on the probabilistic analysis, the undiscounted and discounted QALY gain were similar at [REDACTED] and [REDACTED] respectively and the corresponding incremental costs was [REDACTED] with the incremental cost-effectiveness ratio (ICER) (using discounted QALY gain) of £325,317.

Table 3: Updated model results based on committee preferences (with PAS)

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained
<i>Committee preferred assumptions (deterministic)</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£324,925
BSC	£29,882	5.53	8.40	-	-		-
<i>Committee preferred assumptions (probabilistic)</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£325,317
BSC	£29,919	5.55	8.43	-	-		-

Abbreviations: BSC, best supportive care; PAS, patient access scheme; QALYs, quality-adjusted life years

2.2.3. ERG scenario

As described in Section 2.2.5 of Addendum 4 to the ERG report, given the baseline hyperphagia severity has now been changed to 100% severe hyperphagia, the ERG conducted a scenario analysis which explored the uncertainty surrounding the severe hyperphagia utility multiplier.

This scenario used an alternative value which was presented in the company's model (■■■■), whereby the revised means with all negative numbers were changed to zero and the same difference between mild/moderate utility multipliers was assumed. The ERG considered this value to be conservative (compared to company's presented base case using vignette study value of ■■■■), as it assumes the same difference that of between mild and moderate utility multipliers (assuming linearity, though in real world the relationship could be non-linear).

This scenario resulted in a 12% decrease from the ERG preferred base case ICER incorporating committee preferred assumptions; these results are reproduced in Table 4. Please note that the new PAS discount was already included in the previous addendum to the ERG report, therefore values in this table are identical to those presented in Addendum 4, Table 5.

Table 4: Updated model results for the scenario

	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained	% Change from committee preferred assumptions
Committee preferred assumptions	■■■■	■■■	■■■	£324,925	-
Scenario: Committee preferred assumptions as per Table 1 + Severe hyperphagia utility multiplier of ■■■■ ^a	■■■■	■■■	■■■	£284,644	-12%

Abbreviations: QALYs, quality-adjusted life years

Note: ^a revised means with all negative numbers changed to zero and assuming same difference between mild and moderate

2.3. Additional results from the revised model

This section presents the additional results from the revised model (incorporating the changes summarised in Table 1) with the new PAS discount included, to facilitate evaluation committee meeting 2 (ECM2). These results were not presented in Addendum 4 of the ERG report.

2.3.1. Cumulative impact of changes to company base case resulting in ERG preferred base case

Table 5 below illustrates the stepwise changes from the company's original base case leading to the current ERG base case (including the company's post-ECD1 changes accepted by ERG). As shown in the table, a 3.5% discount rate for health benefits and costs as well as utility multipliers for hyperphagia have the largest incremental impact on the ICER.

Table 5: Incremental impact of changes - ERG base case

	Scenario	Incremental cost	Incremental QALYs (Discounted)	ICER
	Company's original base case – overall/pooled population (without revised PAS for setmelanotide)	████████	14.81	£176,913
	ERG base case (with revised PAS for setmelanotide)			
Committee preferred assumptions	Population: overall population (LEPR, POMC, children and adults combined)	████████	14.81	£118,565
	Hyperphagia: treatment effect applied as a half-cycle correction in the first cycle	████████	14.75	£119,090
	Separate doses for adults and children and by deficiency	████████	14.75	£134,195
	Mortality rate non-responders & BSC: Life expectancy converted to equivalent HR multiplier	████████	14.69	£134,724
	1% discontinuation rate every cycle through lifetime (12 week onwards)	████████	12.71	£140,257
	Utility multipliers for hyperphagia using the following values: a. Mild and moderate hyperphagia: vignette study values b. Severe hyperphagia: -0.33 accepting uncertainty remained	████████	10.22	£174,316
	Discount rate of 3.5% for both health benefits and costs	████████	5.80	£307,018

	Scenario	Incremental cost	Incremental QALYs (Discounted)	ICER
Companies changes post-ECD1 accepted by ERG	Long-term assumption of BMI maintenance for POMC	██████	5.78	£308,072
	100% of patients have severe hyperphagia	██████	5.88	£302,944
	Mean age adjusted for early diagnosis	██████	5.77	£317,133
	50:50 split for paediatrics vs adults distribution	██████	6.05	£314,375
	20:80 split for POMC/PCSK1 vs LEPR distribution	██████	5.87	£324,925

Abbreviations: ECD1, evaluation committee decision 1; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; PAS, patient access scheme; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

2.3.2. Revised ERG base case results for subgroups

As requested by NICE, Table 6 presents the revised ERG base case results (including all of the changes listed in Table 5, apart from the 50:50 split between adult and paediatric patients and the 20:80 split for POMC and LEPR deficiency). Table 7 presents the revised ERG base case results (including only the committee preferences) by deficiency and age subgroups.

It should be noted that the changes have a greater impact on the LEPR deficiency subgroups when compared to the POMC deficiency subgroups, owing to the differences in baseline characteristics of the deficiency subgroups as well as the differential treatment effectiveness of setmelanotide by deficiency subgroup. This has been reflected in the ERG base case ICER for the pooled population (as the LEPR deficiency subgroups constitutes █████ of the pooled population, the pooled population ICER is driven by that of the LEPR deficiency subgroups).

Table 6: Revised ERG base case results by subgroups (with committee preferences and post-ECD1 changes)

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained
<i>POMC paediatric</i>							
Setmelanotide + BSC	████████	████	████	████████	██	████	£264,980
BSC	£42,765	9.02	16.46	-	-		-
<i>POMC adult</i>							
Setmelanotide + BSC	████████	████	████	████████	██	████	£273,606
BSC	£41,203	7.44	12.11	-	-		-
<i>LEPR paediatric</i>							
Setmelanotide + BSC	████████	████	████	████████	██	████	£355,503
BSC	£29,265	6.30	9.43	-	-		-
<i>LEPR adult</i>							
Setmelanotide + BSC	████████	████	████	████████	██	████	£331,160
BSC	£24,447	3.41	4.42	-	-		-

Abbreviations: BSC, best supportive care; ECD1, evaluation committee decision 1; ERG, evidence review group; LEPR, leptin receptor; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

Table 7: Revised ERG base case results by subgroups (with only committee preferences)

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained
<i>POMC paediatric</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£274,858
BSC	£41,504	8.76	15.42	-	-		-
<i>POMC adult</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£276,455
BSC	£38,619	7.07	11.14	-	-		-
<i>LEPR paediatric</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£328,123
BSC	£27,166	5.76	8.33	-	-		-
<i>LEPR adult</i>							
Setmelanotide + BSC	██████	████	████	██████	████	████	£317,815
BSC	£21,396	3.00	3.79	-	-		-

Abbreviations: BSC, best supportive care; ERG, evidence review group; LEPR, leptin receptor; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

2.3.3. Additional ERG scenarios

Per the request from NICE, the ERG conducted the following additional scenarios using the revised model:

- Pediatric versus adult population split as per committee preference (74:26); and
- Severe hyperphagia utility multiplier presented by the company with all negative values changed to zero.

The results of the additional scenario analyses are presented in Table 8. As expected, the impact of the committee preferred split regarding the pediatric versus adult population was observed to be minor (1% increase from current ERG base case) whereas the impact of using severe hyperphagia utility multiplier of ■■■ was larger (23% reduction from current ERG base case).

Table 8: Additional ERG scenarios using revised model

	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per (discounted) QALY gained	% Change from committee preferred assumptions
ERG base case	■■■■	■■	■■■	£324,925	-
<i>Paediatric vs. adult split scenario</i>					
Scenario: Committee preferred assumptions as per Table 1 + Paediatric vs. adult split as per committee preference (74:26)	■■■■	■■	■■■	£328,924	1%
<i>Severe hyperphagia utility multiplier scenario</i>					
Scenario: Committee preferred assumptions as per Table 1 + Severe hyperphagia utility multiplier of ■■■ ^a	■■■■	■■	■■■	£251,269	-23%

Abbreviations: ERG, evidence review group; QALYs, quality-adjusted life years; vs., versus

Note: ^a revised means with all negative numbers changed to zero



Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

A Highly Specialised Technology Appraisal

Addendum #6

Additional analyses requested by NICE following the second evaluation consultation meeting

27 April 2022

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1. INTRODUCTION

The purpose of this addendum is to provide NICE with additional information following its second evaluation consultation meeting (ECM2).

The Evidence Review Group (ERG) was requested to provide an incremental cost-effectiveness ratio (ICER), along with discounted and undiscounted quality-adjusted life years (QALYs), using committee preferred assumptions, changes to the ERG base case post-ECD1 as well as assumptions not included in the ERG base case at ECM2 (see Table 1).

These assumptions comprised the inclusion of a carer disutility from the appraisal of metreleptin for treating lipodystrophy (HST14) and using a severe hyperphagia utility multiplier value from the company's scenario, which normalised negative values from its vignette study, but without applying the same difference between mild and moderate hyperphagia. Furthermore, NICE requested that the ERG provides a scenario that includes these assumptions, but with all patients entering the model as children (see Tables 3a and 3b).

Carer disutility is calculated under two assumptions for the intervention arm: 1. All patients incur a carer disutility 'penalty' and 2. Only non-responding patients incur a carer disutility. All patients are assumed to incur the carer disutility in the control arm. This is important because the company's original response to the ECD was ambiguous as to their intent in implementing the carer disutility. Under assumption 1, the absolute difference between arms in total QALYs is not affected, but the relative difference in QALYs is. Under assumption 2, the absolute difference between arms in total QALYs is affected, thus altering ICERs. In other words, under assumption 2, the treatment is modelled to impact QALYs in part by impacting carer disutilities.

In addition, in implementing the carer disutility, the ERG implemented an adjustment to the company's approach. The company added carer disutility to the model by subtracting a constant penalty of [REDACTED] to QALYs accrued by patient-carer dyads each year in the non-responder health state and for all patients receiving BSC (i.e., comparator arm). However, the company placed a lower limit of accrued QALYs in the health states at zero. This is incorrect as once the QALYs accrued by the patient are below [REDACTED] per year, it systematically reduces the quality of life (QoL) burden estimate on the carers which (1) is implausible, and (2) contradicts the claimed constant decrement.

Note that this issue occurred because whilst patient quality of life is measured in the *utility* of a health state, for ease of modelling the company measured caregiver burden in terms of *disutility*. Negative QALY accruals will be correctly accounted for in the incremental analysis. The ERG has therefore removed the lower floor to allow negative QALY accruals in non-responder and BSC health states.

2. ERG RESPONSE

2.1. Additional analyses requested by NICE following ECM2

The complete list of assumptions requested by NICE to inform the committee's decision-making are summarised in Table 1 below.

Table 1: Assumptions requested by NICE to inform the committee's decision-making following ECM2

Committee preferred assumptions in ERG base case	Overall population (LEPR, POMC, children and adults combined)
	Hyperphagia treatment effect: half-cycle correction in first cycle
	Separate doses for adults and children and by deficiency
	Mortality rate non-responders & BSC: life expectancy converted to equivalent HR multiplier
	1% discontinuation rate (12 week onwards)
	Utility multipliers for mild and moderate hyperphagia: vignette study values
	Discount rate of 3.5% for both health benefits and costs
Changes post-ECM2 in ERG base case	Long-term assumption of BMI maintenance for POMC
	All patients have severe hyperphagia at baseline
	Mean age adjusted for early diagnosis
	ECM2 split for paediatrics vs adults distribution
	ECM2 split for POMC/PCSK1 vs LEPR distribution
Not in ERG base case ECM2, requested by NICE post-ECM2	Inclusion of carer disutility for HST14
	Utility multipliers for severe hyperphagia: utility value from company's scenario normalizing negative values from the vignette study to zero but without applying the same difference between mild and moderate hyperphagia

Abbreviations: BMI, body mass index; BSC, best supportive care; ECM2, evaluation consultation meeting 2; ECD1, evaluation committee decision 1; ERG, Evidence Review Group; HR, hazard ratio; HST, highly specialised technology; LEPR, leptin receptor; NICE, National Institute for Health and Care Excellence; PCSK1, proprotein convertase subtilisin/kexin 1; POMC, proopiomelanocortin; vs, versus

ICERs for the entire population are presented in the tables below: Table 2a details the results based on NICE's listed assumptions with all patients incurring the carer disutility; Table 2b details the results based on NICE's listed assumptions with only non-responder patients incurring carer disutility.

Table 2a: Results based on NICE’s listed assumptions following ECM2. All patients incur carer disutility

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per QALY gained (Discounted)
<i>Deterministic results</i>							
Setmelanotide + BSC	██████	██	██				
BSC	██████	██	██	██████	██	██	£251,269

Abbreviations: BSC, best supportive care; ECM2, evaluation consultation meeting 2; QALY, quality-adjusted life years

Table 3b: Results based on NICE’s listed assumptions following ECM2. Only non-responder patients incur carer disutility

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per QALY gained (Discounted)
<i>Deterministic results</i>							
Setmelanotide + BSC	██████	██	██				
BSC	██████	██	██	██████	██	██	£194,630

Abbreviations: BSC, best supportive care; ECM2, evaluation consultation meeting 2; QALY, quality-adjusted life years

2.2. Scenario assuming all patients entering the model are paediatric

As per the NICE request following ECM2, the ERG has conducted a scenario analysis which incorporates all of the listed assumptions detailed in Table 1. This scenario assumes that all patients entering the model are paediatric. Both discounted and undiscounted QALY gains have been provided in the tables below: Table 3a details the scenario with all patients incurring the carer disutility; Table 3b details the scenario with only non-responder patients incurring the carer disutility.

Table 4a: Scenario analysis assuming all patients entering the model are paediatric. All patients incur carer disutility

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per QALY gained (Discounted)
<i>Deterministic results</i>							
Setmelanotide + BSC	██████	████	████				
BSC	████	████	████	██████	████	████	£241,736

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life years

Table 5b: Scenario analysis assuming all patients entering the model are paediatric. Only non-responder patients incur carer disutility

	Total costs (Discounted)	Total QALYs (Discounted)	Total QALYs (Undiscounted)	Incremental costs (Discounted)	Incremental QALYs (Discounted)	Incremental QALYs (Undiscounted)	Cost per QALY gained (Discounted)
<i>Deterministic results</i>							
Setmelanotide + BSC	██████	████	████				
BSC	████	████	████	██████	████	████	£187,224

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life years