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

Highly Specialised Technologies Evaluation Programme

Produced by

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Table of Contents

List of tables

List of Figures

Abbreviations

ACTH	adrenocorticotropic hormone
AE(s)	adverse event(s)
AgRP	agouti-related protein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIA	bioelectrical impedance
BMI	body mass index
BSC	best supportive care
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CS	company submission
CSR	clinical study report
CV(D)	cardiovascular (disease)
DBP	diastolic blood pressure
DEXA	dual-energy x-ray absorptiometry
DUS	designated use set
eMIT	electronic Market Information Tool
EQ-5D	EuroQol 5 dimension
ERG	Evidence Review Group
FAS	full analysis set
FDA	Food and Drug Administration
GDG	guideline development group
HbA1c	haemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
HST	highly specialised technology
HTA	health technology assessment
ICER(s)	incremental cost-effectiveness ratio(s)
ISR	injection-site reaction
ITT	intention-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life-Lite

ACTH	adrenocorticotropic hormone
KOL	key opinion leader
LDL-C	low-density lipoprotein cholesterol
LEPR	leptin receptor
LoF	loss of function
LYG	life years gained
MC1R	melanocortin-1 receptor
MC3R	melanocortin-3 receptor
MC4R	melanocortin-4 receptor
MHRA	Medicines and Healthcare products Regulatory Agency
MSH	melanocyte-stimulating hormone
NA	not applicable
NAFLD	non-alcoholic fatty liver disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NPY	neuropeptide Y
NR	not reported
OGTT	oral glucose tolerance testing
OSA	Obstructive sleep apnoea
OWSA	one-way sensitivity analysis
PCSK1	proprotein convertase subtilisin/kexin type 1
PedsQL	Paediatric Quality of Life Inventory
PHQ-9	Patient Health Questionnaire-9
POMC	Proopiomelanocortin
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	quality assessment
QALY(s)	quality-adjusted life year(s)
QoL	quality of life
RCT	randomised controlled trial
RGDO(s)	rare genetic disorder(s) of obesity
RWE	real-world evidence
SAE(s)	serious adverse event(s)

ACTH	adrenocorticotropic hormone
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SF-10	10-Item Health Survey for Children
SF-12	12-Item Short Form Survey
SF-36	36-Item Short Form Health Survey
SLR	systematic literature review
T2DM	type 2 diabetes mellitus
TA	Technology Appraisal
TC	total cholesterol
TEAE(s)	treatment-emergent adverse event(s)
TG	triglycerides
TTO	time trade-off
Vs	versus
WHO	World Health Organisation
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail, and Section 1.7 presents the preferred assumptions of the ERG. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the key issues in the clinical effectiveness evidence

Table 1: Summary of key issues

ID[3764]	Summary of issues	Report sections
#1	Company decision problem excluded some outcomes from the NICE scope	Sections 1.3 and 2.3
#2	Company trials did not report all outcomes in company decision problem	Sections 1.4 and 3.2.2.5
#3	No direct or indirect evidence presented comparing setmelanotide with standard management in a population of obesity associated with POMC and/or LEPR deficiency	Sections 1.4 and 3.4
#4	Dosing in the included trials is not consistently in accordance with the intended UK dosing	Sections 1.4 and 3.2.2.3
#5	Discount of 1.5% applied to setmelanotide treatment benefit is not appropriate	Sections1.5, 4.2.5 and 6.2.9
#6	Subgroup results are more appropriate for decision making	Sections 1.5, 4.2.3 and 6.2.9
#7	The dose used in the base case analysis was not considered to be appropriate	Sections 1.5, 4.2.6.6 and 6.2.9
#8	The model did not include treatment discontinuation	Sections 1.5, 4.2.6.2 and 6.2.9

ID[3764]	Summary of issues	Report sections
#9	There is uncertainty surrounding the clinical data used in the economic model and approach used to extrapolate mortality and long-term treatment effectiveness	Sections 1.6, 4.2.6.1, 4.2.6.3, 6.2.1, 6.2.4 and 6.2.9
#10	There is uncertainty surrounding modelled hyperphagia inputs	Sections 1.6, 4.2.6.1, 4.2.6.5 and 6.2.9

Abbreviations: HRQoL, health-related quality of life; LEPR, leptin receptor; NICE, National Institute for Health and Care Excellence; POMC, proopiomelanocortin

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are as follows:

- The ERG considered that a discount of 1.5% applied to the setmelanotide treatment benefit is not appropriate, as a non-reference case of restoring participants to full or near-full health was not demonstrated with empirically-derived data. As mortality was fully modelled and based on assumption and clinical opinion, the ERG considered the NICE reference case discount of 3.5% to be more appropriate. See Section 4.2.6.3 and Section 6.2.9.
- The ERG did not consider patients with POMC and LEPR deficiency obesity, or adult and paediatric patients with either of these conditions, to be sufficiently homogenous to treat as an overall population in the model. The ERG's preferred base case would be to treat these as four subpopulations. See Section 4.2.3 and Section 6.2.9.
- The ERG considered the 'overall' dose used in the company's base case as not appropriate for use in the model, given that separate doses were used during the studies for adult and paediatric patients; and will be used in clinical practice. See Section 6.2.9.
- The ERG did not consider the omission of treatment discontinuation from the model to be appropriate as clinical advice to the ERG indicated that a proportion of patients in practice are likely to discontinue treatment due to adverse events and/or burden of daily administration. See Section 6.2.9.
- The ERG considered there to be uncertainty surrounding the clinical data used in the economic model and approach used to extrapolate mortality and long-term treatment effectiveness. For clinical effectiveness, key parameter values in the economic model were largely informed by short term trial data, proxy data from general obesity population,

assumption and/or clinical expert opinion. For mortality, there was no empirically observed data from trials. See Sections 4.2.6.1, 4.2.6.3, 6.2.1, 6.2.4 and 6.2.9.

- The ERG considered that there is uncertainty around modelled hyperphagia inputs. Baseline hyperphagia values showed a discrepancy with values provided to the ERG by clinical experts, the exact approach to calculating transition probabilities for hyperphagia is unclear and hyperphagia utility values were based on responses from members of the UK general public. See Sections 4.2.6.5 and Section 6.2.9.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Setmelanotide is modelled to reduce patient BMI/BMI Z-scores and result in maintained weight loss over time. Patients with lower BMI/BMI Z-scores have higher utility values and lower mortality rates and experience fewer comorbidities compared to those on best supportive care (BSC).

- Setmelanotide treated patients are modelled to experience an improvement in hyperphagia status. Patients receiving BSC therefore experience higher hyperphagia disutility compared to those on setmelanotide.

- Due to the modelled assumptions with respect to mortality, setmelanotide resulted in an incremental life year gain compared to BSC.

Overall, the technology is modelled to affect costs through the following assumption:

- As setmelanotide is provided in addition to BSC and due to the high acquisition cost of treatment, setmelanotide results in an incremental cost compared to BSC. Costs associated with monitoring and co-morbidity related costs are not considered key drivers of cost effectiveness in this appraisal.

The modelling assumptions that have the greatest effect on the ICER are:

- Using a 3.5% discount rate for benefits

- Reducing the time horizon to 20 years
- Assuming no mortality benefit for responders
- Using alternative hyperphagia assumptions with respect to baseline distribution, transition probabilities and utility values
- Estimating drug costs for setmelanotide based on adult and paediatric specific dosing from the trial
- Using an alternative treatment efficacy assumption after trial duration, i.e. BMI regain

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issues for the committee's consideration.

Key Issue 1: Company decision problem excluded some outcomes from the NICE scope

Report sections	**Sections 1.3 and 2.3**
Description of issue and why the ERG has identified it as important	The ERG noted that the company scope excluded certain outcomes specified in the NICE scope. HRQoL for carers was excluded from the company scope. Also, the scope of co-morbidities was narrowed from the NICE scope, and cancer excluded. The exclusion of HRQoL for carers precludes a full perspective on the psychosocial burden of the condition. The narrowing of the outcome scope with regard to co-morbidities precludes a full perspective on the clinical manifestation of the condition. This increases uncertainty regarding clinical effectiveness.
What alternative approach has the ERG suggested?	The company could have retained the decision problem for outcomes as specified by the NICE scope. The ERG did not consider the non-availability of data in the trials to be sufficient justification for exclusion of outcomes from the NICE scope.
What is the expected effect on the cost-effectiveness estimates?	The reversal of the narrowing of the scope could allow additional data to be considered once available through longer-term follow-up. This could enable observed co-morbidity data from the trial – as well as HRQoL for carers if this outcome can be added in a further follow-up – to inform the economic model. This would likely improve estimation of cost-effectiveness. However, the

Report sections	Sections 1.3 and 2.3
	expected impact on cost-effectiveness estimates remains unknown at this stage.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up, such as the intended five year follow-up for the extension study RM-493-022, as opposed to the presented two year follow-up, could help resolve this uncertainty.

Abbreviations: ERG, Evidence Review Group; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issue for consideration by the committee.

Key Issue 2: Company trials did not report all outcomes in company decision problem

Report sections	Sections 1.4 and 3.2.2.5
Description of issue and why the ERG has identified it as important	The ERG noted that the trials included by the company did not provide data for all outcomes in the company decision problem. Outcome data for mortality, cardiovascular events and scoped co-morbidities were not reported in the included trials. The absence of data for these outcomes in the decision problem increases uncertainty regarding the clinical effectiveness of setmelanotide. The inability to use data observed from the clinical trials for these parameters in the economic model increased uncertainty in the clinical inputs to the model.
What alternative approach has the ERG suggested?	The ERG considered that the short follow-up periods in the included trials are likely to have precluded collection of data on these important outcomes of mortality, cardiovascular events and a wider range of co-morbidities. The company could have fulfilled the intended five-year follow-up period on the extension trial RM-493-022, rather than truncating follow-up at two years.
What is the expected effect on the cost-effectiveness estimates?	The collection of data on these outcomes in the decision problem would enable directly observed data from the company's trials to inform these parameters in the economic model. The absence of data in the trials on mortality, cardiovascular events and scoped co-morbidities increases uncertainty regarding cost-effectiveness estimates. However, the expected impact on cost-effectiveness estimates remains unknown at this stage.

Report sections	Sections 1.4 and 3.2.2.5
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up, such as the intended five year follow-up for the extension study RM-493-022, as opposed to the presented two year follow-up, could help resolve this uncertainty.

Abbreviations: ERG, Evidence Review Group

Key issue 3: No direct or indirect evidence presented comparing setmelanotide with standard management in a population of obesity associated with POMC and/or LEPR deficiency

Report sections	Sections 1.4 and 3.4
Description of issue and why the ERG has identified it as important	No direct or indirect evidence was available to compare setmelanotide and standard management in the appraisal population. This means that there are no data comparing the intervention with the only comparator in the company decision problem – standard management – in patients with obesity associated with POMC or LEPR deficiency. It should also be noted that setmelanotide was co-administered with standard management in the trials, as noted in the company decision problem. While this was not inappropriate in terms of how setmelanotide may be used in future clinical practice, it was problematic for generating clinical effectiveness estimates comparing the intervention and comparator in the decision problem.
What alternative approach has the ERG suggested?	The ERG considered that trial evidence comparing setmelanotide with standard management in a two-arm design would be required to resolve this uncertainty.
What is the expected effect on the cost-effectiveness estimates?	In the absence of this information, there is considerable uncertainty about the relative clinical effectiveness of the intervention and the comparator. This is heightened by the absence of published data relating to the clinical effectiveness of standard management in a population of people with obesity related to POMC or LEPR deficiency. This in turn precludes the use of an indirect treatment comparison. There is great uncertainty relating to the clinical effectiveness of setmelanotide for this indication. This leads to uncertainty regarding the estimates produced by the economic model. However, the expected impact on cost-effectiveness estimates remains unknown at this stage.
What additional evidence or analyses might help to resolve this key issue?	The availability of trial evidence comparing setmelanotide with standard management in a two-arm design would resolve this uncertainty. In the absence of this evidence, this would remain

Report sections	Sections 1.4 and 3.4
	an area of great uncertainty in the clinical effectiveness evidence, which impacts upon the confidence that can be held in the estimates generated by the economic model.

Abbreviations: ERG, Evidence Review Group; LEPR, leptin receptor; POMC, proopiomelanocortin

Key issue 4: Dosing in the included trials is not consistent in accordance with the intended UK dosing

Report sections	Sections 1.4 and 3.2.2.3
Description of issue and why the ERG has identified it as important	All patients in the long-term extension trial RM-493-022 were from Germany, where the maximum dose allowed was 2.5 mg. Therefore, there is no long-term evidence available at the scoped maximum dose of 3.0 mg. This lack of evidence results in considerable uncertainty around the long-term clinical efficacy of the 3.0 mg dose, increasing the uncertainty of cost-effectiveness estimates. Additionally, there are no data on the safety of setmelanotide at a dose of 3.0 mg for longer than 48 weeks. This may have an impact on the real-world use of the drug.
What alternative approach has the ERG suggested?	The company should have ensured that there was a more diverse group of patients participating in the extension trial. The index trials were all international, and all had patients from countries where the maximum dose matched the company's scoped maximum dose of 3.0 mg. Because of limitations by regulatory authorities, German patients could only have their dose titrated up to 2.5 mg. Further long-term trials including patients on a 3.0 mg dose would resolve this uncertainty.
What is the expected effect on the cost-effectiveness estimates?	With the absence of this information, there is uncertainty around the benefits of patients taking the higher dose of 3.0 mg for a longer period of time. Additionally, because long-term adverse events associated with a dose of 3.0 mg are unknown, the discontinuation rates of the patients are highly uncertain, which have a knock-on impact on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Further long-term trials or real-world data collection involving patients being treated with a 3.0 mg dose would resolve this uncertainty.

1.5. The cost effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the company health economic evidence and economic evaluation presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 5: Discount of 1.5% applied to setmelanotide treatment benefit is not appropriate

Report sections	Section 1.5, Section 4.2.5 and Section 6.2.9
Description of issue and why the ERG has identified it as important	The company discounted treatment benefits by 1.5% in their base case analysis, and justified this on the basis that NICE considers non-reference case discounting when a technology restores people, who would otherwise die or have a very severely impaired life, to full or near full health (and when this is sustained over a very long period, normally 30 years). The ERG did not consider this to be appropriate given that mortality data used in the model were not derived from robust clinical data, but rather from assumption and clinical opinion (see Section 4.2.6.3 for further discussion).
What alternative approach has the ERG suggested?	Due to the uncertainty surrounding modelled mortality estimates, the ERG consider that 3.5% should be used as the appropriate discount rate for treatment benefits.
What is the expected effect on the cost-effectiveness estimates?	Applying the NICE reference case discount (3.5%) to treatment benefits has a substantial upward impact on the ICER (see Section 6.2.9).
What additional evidence or analyses might help to resolve this key issue?	Treatment effectiveness and mortality data collected from long term direct head to head studies (comparing setmelanotide to BSC) would help to address uncertainty surrounding the incremental life year gain associated with setmelanotide.

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year

Key Issue 6: Subgroup results are more appropriate for decision making

Report sections	Section 1.5, Section 4.2.3 and Section 6.2.9
Description of issue and why the ERG has identified it as important	In addition to presenting base case results for POMC and LEPR populations separately, the company presented cost effectiveness results for an overall population i.e. a single ICER was provided for POMC/LEPR patients. Based on clinician input to the ERG, an overall population was not considered to be appropriate, given that there are differences in treatment effect and

Report sections	Section 1.5, Section 4.2.3 and Section 6.2.9
	natural disease progression between POMC/PCSK1 and LEPR patients (and differences in disease state between adult and paediatric patients). Furthermore, the overall results do not represent a clinically plausible patient group. The company provided subgroup analyses results stratified according to whether the patient had POMC or LEPR and whether the patient was adult or paediatric. Results for the following four subgroups were provided by the company and presented in the CS. • LEPR (paediatric) • LEPR (adult) • POMC (paediatric) • POMC (adult) The ERG considered the subgroup analyses results to be more reasonable for consideration, as these results acknowledge/represent differences in POMC/PCSK1 and LEPR status as well as patient age (see Section 4.2.3). However it should be noted that there may be some concerns surrounding the robustness of results, due to the small patients number used in the these analyses.
What alternative approach has the ERG suggested?	Consideration of subgroup results, stratified according to disease type and age.
What is the expected effect on the cost-effectiveness estimates?	The ICER varied according to subgroup. See Section 6.2.9
What additional evidence or analyses might help to resolve this key issue?	Larger clinical trials (with increased patient numbers) would result in more robust cost effectiveness results. However, the ERG acknowledge the rare nature of POMC/PCSK1 and LEPR deficiency obesity.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; PCSK1; proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Key Issue 7: The dose used in the base case analysis was not considered to be appropriate

Report sections	Section 1.5, Section 4.2.6.6 and Section 6.2.9
Description of issue and why the ERG has identified it as important	In the base case analysis, setmelanotide treatment costs in Year 1 were estimated to be [redacted]/day. This was based on the average therapeutic dose observed in the clinical studies RM-493-012 and RM-493-015 i.e. based on adult and paediatric doses. For Years 2+, the company estimated the dose to be [redacted]/day based on the

Report sections	Section 1.5, Section 4.2.6.6 and Section 6.2.9
	average therapeutic dose at the end of the study period in RM-493-012 and RM-493-015. The company stated that the overall average dose for patients was used in the economic analysis due to the small number of patients in each subpopulation, which would further add to uncertainty. The ERG accepted that small patient numbers add uncertainty surrounding the most appropriate dose, however the ERG did not consider an average 'overall' dose to be appropriate for use in the model, given that separate doses were used during the studies for adult and paediatric patients, and will be used in clinical practice. As such, setmelanotide treatment costs are likely to differ for both adult and paediatric patients.
What alternative approach has the ERG suggested?	During clarification the ERG asked the company to provide the average dose for adult and paediatric patients separately within each study. The company subsequently provided this information and updated their economic model to allow the user to select the setmelanotide dose separately. The average dose was stratified according to POMC/LEPR and patient age: • POMC paediatric: [redacted]/day • POMC adult: [redacted]/day • LEPR paediatric: [redacted]/day • LEPR adult: [redacted]/day
What is the expected effect on the cost-effectiveness estimates?	The use of adult and paediatric specific dosing had an upward impact on results (see Section 6.2.9).
What additional evidence or analyses might help to resolve this key issue?	Larger clinical trials would result in more robust cost effectiveness results and help to inform model dosing. However, the ERG acknowledged the rare nature of POMC/PCSK1 and LEPR.

Abbreviations: ERG, Evidence Review Group; LEPR, leptin receptor; PCSK1; proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Key Issue 8: The model did not include treatment discontinuation

Report sections	Section 1.5, Section 4.2.6.2 and Section 6.2.9
Description of issue and why the ERG has identified it as important	In the base case analysis the company assumed that all responders to setmelanotide remain on treatment for the duration of their lives i.e. treatment discontinuation was not modelled.

Report sections	Section 1.5, Section 4.2.6.2 and Section 6.2.9
	Based on clinician input to the ERG, this assumption was not considered to be appropriate as a proportion of patients in practice are likely to discontinue treatment due to adverse events and/or burden of daily administration.
What alternative approach has the ERG suggested?	In order to determine the impact of treatment discontinuation on the ICER, the ERG has conducted a scenario analysis which modelled a 1% discontinuation rate throughout the modelled time horizon.
What is the expected effect on the cost-effectiveness estimates?	This scenario analysis resulted in a minor upward increase in the ICER. See Section 6.2.9.
What additional evidence or analyses might help to resolve this key issue?	Longer term clinical data or RWE would help to inform modelled discontinuation over time.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; RWE, real-world evidence

1.6. Other key issues: summary of the ERG's views

Key Issue 9: There is uncertainty surrounding the clinical data used in the economic model and approach used to extrapolate mortality and long-term treatment effectiveness

Report sections	Sections 1.6, 4.2.6.1, 4.2.6.3, 6.2.1, 6.2.4 and 6.2.9
Description of issue and why the ERG has identified it as important	Clinical effectiveness uncertainty • The ERG noted there to be a paucity of robust setmelanotide treatment effectiveness data in patients with POMC/PCSK1 and LEPR. As such key parameter values in the economic model were largely informed by short term trial data, proxy data from general obesity population, assumption and/or clinical expert opinion. The ERG considered these sources to introduce uncertainty, however due to the paucity of data associated with this condition more robust data did not appear available for use in the model. See Section 4.2.6.1 for further discussion, regarding uncertainty surrounding modelled clinical effectiveness. Mortality uncertainty • The ERG noted there to be a paucity of mortality data in patients with POMC/PCSK1 and LEPR. In the base case analysis, average and maximum age life expectancy for POMC and LEPR non-

Report sections	Sections 1.6, 4.2.6.1, 4.2.6.3, 6.2.1, 6.2.4 and 6.2.9
	responders/patients on BSC, were derived from clinical opinion. The ERG considered that the lack of mortality data in POMC/PCSK1 and LEPR patients introduces uncertainty into the economic analysis. Additionally, the ERG identified concerns surrounding the company's inconsistent approach to estimating mortality for responders and non-responders in the model. See Section 4.2.6.3 for further discussion.
What alternative approach has the ERG suggested?	To test uncertainty surrounding modelled clinical effectiveness and mortality, the ERG conducted scenario analyses using alternative assumptions. See Sections 6.2.1 and 6.2.4.
What is the expected effect on the cost-effectiveness estimates?	Results were sensitive to certain alternative mortality assumptions including the use of increased life expectancy estimates for non-responders and assuming no difference in mortality between responders and non-responders. See Section 6.2.9.
What additional evidence or analyses might help to resolve this key issue?	Mature clinical trial data or retrospective real world data in patients with POMC/PCSK1 and LEPR would help to resolve uncertainty surrounding long term treatment effectiveness and mortality.

Abbreviations: BMI, body mass index; CS, company submission; CSR, clinical study report; ERG, Evidence Review Group; LEPR, leptin receptor; PCSK1; proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Key Issue 10: There is uncertainty surrounding modelled hyperphagia inputs

Report sections	Section 1.6, Section 4.2.6.1, Section 4.2.6.5 and Section 6.2.9
Description of issue and why the ERG has identified it as important	The ERG identified hyperphagia to be a key driver of the incremental QALY gain associated with setmelanotide and understood this to be modelled primarily via three pathways i.e. baseline hyperphagia distribution, hyperphagia transition probabilities and hyperphagia utility multipliers (see Sections 4.2.6.1 and 4.2.6.5). 1. Baseline hyperphagia distribution Baseline distribution of hyperphagia in the model did not appear to be aligned with or estimated using the health state descriptions outlined in the company's vignette study, but rather clinical opinion. Furthermore, the company did not provide sensitivity analyses which varied baseline hyperphagia distribution.

Report sections	Section 1.6, Section 4.2.6.1, Section 4.2.6.5 and Section 6.2.9
	2. Hyperphagia transition probabilities The ERG noted that hyperphagia transition probabilities were based on an internal analysis by the company and details were not provided in the CS with respect to their calculation. As such, the ERG considered there to be considerable uncertainty surrounding the impact of setmelanotide on hyperphagia. 3. Hyperphagia utility values The impact of hyperphagia on utility was not captured in the pivotal trials, but rather the company conducted a vignette study which resulted in the estimation of utility multipliers for mild moderate and severe hyperphagia. A TTO approach was used and values were based on responses from members of the UK general public (not patients with POMC/PCSK1 and LEPR). Overall, the ERG considered the lack of robust hyperphagia data in patients with POMC/PCSK1 and LEPR deficiency to be a key area of uncertainty within this appraisal.
What alternative approach has the ERG suggested?	The ERG conducted a combined scenario analyses which varied key hyperphagia model inputs including baseline hyperphagia distribution, hyperphagia transition probabilities and hyperphagia utility multipliers. See Section 6.2.9 for further description and results.
What is the expected effect on the cost-effectiveness estimates?	This scenario analysis had a moderate to large impact on the ICERs. See Section 6.2.9.
What additional evidence or analyses might help to resolve this key issue?	Hyperphagia data collected directly from patients, would help to address uncertainty with respect to modelled estimates.

Abbreviations: CS, company submission; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; PCSK1; proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Health Survey; TTO, time trade-off

1.7. Summary of ERG's preferred assumptions and resulting ICER

The results based on ERG preferred base case assumptions have been outlined for each of the subpopulations in Table 2 to Table 5. The company resolved an identified error regarding the hyperphagia related treatment effect assumption in response to the ERG clarification question B11 and provided an updated model. See Section 4.2.6.1 and Section 6.1.

Table 2: Summary of ERG's preferred assumptions and ICER (LEPR, paediatric)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£165,424
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£166,843
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£215,295
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£233,466
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£230,521
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	**£373,041**

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; QALY, quality-adjusted life year

Table 3: Summary of ERG's preferred assumptions and ICER (LEPR, adult)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£181,769
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£183,648
ERG's preferred base case				
Setmelanotide dose based on average adult dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£253,357
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£257,215
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£261,462
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	**£407,126**

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR. leptin receptor; QALY, quality-adjusted life year

Table 4: Summary of ERG's preferred assumptions and ICER (POMC, paediatric)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£191,348

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£193,008
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£160,076
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£166,888
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£164,045
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	**£273,366**

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Table 5. Summary of ERG's preferred assumptions and ICER (POMC, adult)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£183,100
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£184,766
ERG's preferred base case				
Setmelanotide dose based on average adult dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£179,070
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£181,835
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£188,335
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	**£303,142**

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

2. BACKGROUND

2.1. Critique of company's description of underlying health problem

The company provided an overview of the burden of obesity caused by leptin-receptor (LEPR) or proopiomelanocortin (POMC) (including proprotein convertase-subtilisin/kexin type-1 (PCSK1)) deficiency in the target population in Section B.6 and B.7 in the CS.

The melanocortin-4 receptor (MC4R) pathway, located in the hypothalamus, contributes to the regulation of energy homeostasis through its effect on satiety and energy expenditure (Eneli et al 2019[1]). Two populations of antagonistic neurons regulate this process: POMC neurons release MC4R-targeted hormones to promote satiety and energy expenditure; agouti-related protein/neuropeptide Y (AgRP/NPY) neurons release AgRP, an inverse agonist of MC4R, to promote food intake (Cansell et al 2012[2]; Eneli et al 2019[1]; Frihauf et al 2010[3]). LEPR and POMC are functional proteins involved in the signalling cascade of POMC neurons upstream of MC4R (Eneli et al 2019[1]); LEPR is additionally involved in AgRP/NPY pathway (Nunziata et al 2019[4]). Deficiencies, or loss of function (LoF), in these key proteins cause disruptions to the MC4R signalling pathway involved in increasing satiety and energy expenditure, leading to hyperphagia and early-onset severe obesity (Ayers et al 2018[5]).

As part of a functional upstream MC4R pathway, leptin, a hormone released into the periphery by adipose tissue and enterocytes, crosses the blood-brain barrier into the hypothalamus. It binds to LEPR on POMC neurons and causes a signalling cascade during which POMC is produced and subsequently cleaved by PCSK1 into α-, β- and γ-melanocyte-stimulating hormone (α-, β-, γ-MSH) and adrenocorticotropic hormone (ACTH) (Eneli et al 2019[1]). These hormone neuropeptides activate MC4R, with α- and β-MSH as well as ACTH showing equal affinity, all greater than γ-MSH, for the receptor (Adan et al 2006[6]). The end results of this activation of MC4R are decreased hunger and food-seeking, and increased expenditure of energy, thereby inhibiting weight gain.

The deficiency, or LoF, of LEPR and POMC (including disruption of POMC processing by PCSK1) proteins is caused by a mutation in alleles of the *LEPR*, *POMC* or *PCSK1* genes encoding for the leptin receptor, the production of the prohormone POMC, or the production of the PCSK1 enzyme, respectively (Kleinendorst et al 2020[7]; Eneli et al 2019[1]; Stijnen et al 2016[8]). These mutations can be homozygous, with two defective alleles at the same loci in the gene, compound heterozygous, with two defective alleles at different loci in the same gene,

heterozygous, affecting only one allele at a gene locus, or composite heterozygous, with two or more defective alleles among two or more of the three genes. These defects are all considered rare genetic disorders of obesity (RGDOs), but mutations affecting both alleles (biallelic mutations), i.e. homozygous and compound heterozygous, result in more severe degrees of obesity when compared to those with heterozygous mutations (Eneli et al 2019[1]). In a study of individuals with MC4R pathway mutations, all homozygotic individuals had severe obesity; only 68% of heterozygotic individuals were severely obese. The authors concluded that the degree of obesity in heterozygotic individuals depends on the extent of remaining functional MC4R expression (Farooqi et al 2003[9]).

Clinical advice to the ERG indicated that LEPR deficiency affects not only the POMC signalling cascade, but likely also the AgRP/NPY signalling cascade to the downstream MC4R. Therefore, circulating leptin would not inhibit AgRP/NPY signalling, resulting in increased food-seeking stimuli in addition to the lack of inhibiting stimuli from POMC signalling. The ERG noted that as a result of this 'double burden', people with LEPR deficiency tend to have increased hyperphagia and more severe obesity than those with POMC deficiency. The ERG noted that the mechanisms involving obesity and hyperphagia of both conditions are largely shared downstream from the POMC neuron, although people with POMC deficiency additionally have adrenal insufficiency and require treatment with steroids. The ERG considered it important to recognise the distinction between these two populations and consider them separately.

RGDOs are often epidemiologically characterised by severe obesity or obesity class III; classified by the National Health Service (NHS) as a body mass index (BMI) of 40.0 kg/m^2 or greater in adults, and BMI ≥99th percentile in children[10-12]. POMC and LEPR deficiency are rare genetic conditions, with 50 and 88 reported global cases respectively[7,13]. The ERG noted that the chapter by Challis[13] cited by the company is marked as retired, meaning that it is unlikely to represent the current clinical reality. The prevalence of obesity associated with POMC and LEPR deficiency in England and Wales cannot be ascertained with any certainty. The company identified around [redacted] patients in England and Wales with obesity associated with POMC/PCSK1 or LEPR deficiency. The ERG considered that expected wider rollout of genetic testing among children with severe obesity is likely to increase the number of diagnosed cases. Nevertheless, the ERG was satisfied to classify these as rare conditions.

The ERG agreed with the company that there are scarce published data to epidemiologically characterise mortality associated with obesity associated with POMC and LEPR deficiency. The

company cites clinical advice indicating that LEPR deficiency is especially associated with a particularly severe form of obesity and that, coupled with LEPR patients' slightly compromised immune function, contributes to a significant mortality rate from respiratory infections, often in childhood. The company noted that some such cases are presented in the literature[14]. Clinical advice to the ERG supported the company's position on this matter.

Limited epidemiological data are also available to characterise the co-morbidities associated with obesity due to POMC and LEPR deficiency. The company suggested that evidence relating to obesity in general may offer useful insight into co-morbidities, although this would be a conservative approach as the conditions are not directly comparable and obesity due to POMC and LEPR deficiency is expected to be associated with a worse co-morbidity profile. Clinical advice to the ERG supported the company's position on this matter. Evidence from a systematic review and meta-analysis[15] shows that obese persons are at an increased risk of co-morbidities including malignancies, cardiovascular disorders and a range of chronic conditions. Separately, obesity in children has been associated with increased risk of obstructive sleep apnoea, impaired lung development, musculoskeletal problems and non-alcoholic fatty liver disease[16,17].

The ERG agreed with the company that there are no published studies assessing the quality of life (QoL) of patients specifically with POMC or LEPR deficiency. The ERG agreed with the company that two key elements affecting QoL in these patients are likely to be obesity itself and hyperphagia, which can impact patients' ability to participate in normal life due to the preoccupation with food. However, clinical advice to the ERG also indicated that skin pigmentation as a result of taking setmelanotide as well as failure to go through puberty associated with LEPR or POMC deficiency and consequent fertility and reproductive health issues as a larger detractor to QoL. There is evidence from obesity in general that co-morbidities associated with obesity are likely to result in poorer QoL compared to otherwise comparable persons without obesity[16]. The ERG agreed with the company that depression and social isolation are important considerations in the impact of obesity on QoL. Obesity and RGDO linked to MC4R pathway gene variants are also associated with the development of depression and social isolation in children and adolescents[18] and general obesity carries a clear social stigma across societies[19].

RGDOs are often poorly diagnosed. This may relate to challenges in differentiating the presenting symptoms of such conditions from more general obesity conditions. Traditionally, the potential of a genetic underpinning to a patient's presenting obesity is only explored following

unsuccessful response to diet and lifestyle advice interventions. Recent adoption of genetic testing for rare genetic obesity conditions in the NHS among children who present with early onset severe obesity could enable earlier commencement of appropriate treatment.

The ERG considered that the company's description of the underlying health problem was generally appropriate and did not identify any specific concerns with regard to how this was described.

2.2. Critique of company's overview of current service provision

The company provides an overview of current treatment options for LEPR and POMC associated obesity, in Section B.8 of the CS.

There are limited treatment options available for persons with LEPR and POMC associated obesity. Clinical guidelines in the UK focus on the management of general obesity. The ERG agreed with the company that there are no current guidelines for the management of RGDOs associated with LEPR or POMC deficiency. The ERG agreed with the company that many recommended treatments for general obesity are neither appropriate, nor effective, for LEPR or POMC associated obesity, because they do not address the impairment of the MC4R pathway[20-23].

There are three NICE Guidelines cited by the company – CG189, NG7, and CG43[12,24,25]. All focus on general obesity, and the relevance to the decision problem addressed in this appraisal is limited. The company outlines the four-tiered organisation of obesity services within NHS England. Tier 1 is classified as 'universal services such as health promotion or primary care'. Tier 2 is classified as 'lifestyle intervention'. Tier 3 is classified as 'specialist weight management services'. Tier 4 is classified as 'bariatric surgery'. Lifestyle and behaviour management form the cornerstone of general obesity treatment guidelines.

The company indicates that the first step of the referral and diagnostic pathway for children with early onset obesity is a consultation with their GP, who may refer them to a paediatric endocrinologist or geneticist based on their extreme early onset obesity and other clinical features such as hyperphagia and/or a family history of extreme obesity. The company indicates that children may then be referred to genetic testing – originally only available in Cambridge but now available as part of a nationally commissioned service through NHS England – but that there is no specific clinical pathway for RGDOs and that treatment is limited to diet and lifestyle advice, which is not effective for this indication due to its genetic aetiology.

The CS provided an overview of the mechanism of setmelanotide (IMCIVREE®) in Section 2.1. Briefly, setmelanotide is a cyclised octapeptide analogue of α-MSH, acting as an MC4R agonist by binding selectively to and activating the MC4R, thereby promoting satiety and consequent weight loss. In this section, the company also describes melanocortin-1 receptor (MC1R) activation in the mediation of melanin accumulation and resultant skin pigmentation in the absence of ultraviolet light, with additional literature sought by the ERG confirming that MC1R are also stimulated by α-MSH produced from POMC upstream (Beaumont et al 2011[26]). The company reports a 20-fold reduced affinity of setmelanotide for MC1R and melanocortin-3 receptors (MC3R) when compared to MC4R. However, the ERG noted that a study by Kanti et al 2021[27] reports changes in hair and skin pigmentation during treatment with setmelanotide which the authors attribute to potential off-target interactions with MC1R. Clinical advice to the ERG further highlighted uncertainties in the binding affinity of setmelanotide for MC1R.

Setmelanotide is administered once daily through subcutaneous (SC) injection in the abdomen, thigh or arm at the beginning of the day, with the company indicating maximised hunger reduction as rationale. The ERG was satisfied that this is reasonable. The CS further indicated in Section 2.2 that people with the condition would receive treatment with setmelanotide for the duration of their lives, though clinical advice to the ERG suggested that some discontinuations may occur over the long term due to the requirement for continuous injections and skin hyperpigmentation due to off-target MC1R interaction. The dosing of setmelanotide follows an up-titration regimen, with a starting dose of 2 mg in adults and 1 mg in paediatric patients for two weeks to assess tolerability. If well tolerated the dose may be increased to 3 mg in adults as well as adolescents (aged 12 to 17) with insufficient weight loss; and may be increased to 2 mg in children younger than 12. The ERG observed, however, that this protocol in the introduction to the CS indicated an intention to have a steeper up-titration protocol in practice than that described in the index trials (start on 1 mg and increase at 0.5 mg increments).The company indicated in Table 2 (p.12) of the CS that dose titration with setmelanotide should be done for people with moderate renal impairment; the use of IMCIVREE® is contraindicated for people with severe renal impairment. The ERG also noted that impaired renal function was an exclusion criterion for trials included in the CS (Tables 12 and 13), though clinical advice indicated that renal damage has been reported in people with LEPR deficiency. This may present a limitation with regards to application but is reflected in the Summary of Product Characteristics; the ERG considered this a known limitation.

The company considered that setmelanotide would be offered alongside rather than as a replacement for standard management of obesity and could be commissioned as part of tier 3 in the NHS England system for the management of obesity. The company considered, based on clinical advice, that this could be rolled out across all Tier 3 centres and also across a planned network of 14 commissioned paediatric centres. The ERG considered that the company's description of current treatment options and pathways was generally accurate and identified no particular issues with how they were characterised.

2.3. Critique of company's definition of the decision problem

The company statement regarding the decision problem is presented in Section A.1 of the CS. The company position and the ERG response is provided in Table 5 below.

The ERG noted in Section 6.2 of the company submission that setmelanotide is only indicated for people with biallelic deficiency of LEPR or POMC confirmed by genetic testing, potentially representing a narrower scope to that provided by NICE, citing BMI ≥ 30 kg/m^2 in adults and weight for age ≥ 97th percentile in adolescents and children. Clinical advice to the ERG confirmed that people eligible for setmelanotide would fall into the scope provided by NICE, as disruptive biallelic mutations represent the most severe cases of genetic obesity. However, clinical advice to the ERG further indicated that 20% of the adult population in the UK has a BMI of 30 kg/m^2 and above, and that some of these individuals would have heterozygous mutations in POMC as heterozygous carriers of POMC deficiency have a tendency toward obesity. This presents an area of uncertainty for generalisability of results from the company submission to the NICE scope.

The ERG further noted that an inclusion criterion for paediatric patients in the included trials was weight ≥ 95th percentile, representing a slight deviation from the NICE scope of ≥ 97th percentile. Following clinical advice to the ERG that some children with rigorously managed food intake, who are otherwise eligible, may fall below the 97th percentile and be excluded by the NICE scope, the ERG considered the minor deviation in scope to be reasonable.

The ERG considered that the evidence presented by the company was broadly consistent with the decision problem, although noted some points of difference, some of which the ERG considered to be justifiable and others which the ERG considered to represent a limitation.

The ERG was satisfied with the company's decision to present setmelanotide in combination with standard treatment, rather than just setmelanotide as per the NICE scope[28], since the

company intends setmelanotide to be administered alongside standard treatment in specialist centres.

The ERG was satisfied with the company's decision to exclude three comparators that are listed in the NICE scope – orlistat, methylcellulose and bariatric surgery – as they are not routinely used in the NHS in England and Wales for this indication.

The ERG however noted that the company had narrowed the decision problem with regard to outcomes in comparison with the NICE scope. The exclusion of health-related quality of life for carers precludes a full perspective on the psychosocial burden of the condition. The narrowing of the outcome scope with regard to co-morbidities precludes a full perspective on the clinical manifestation of the condition. The narrowed scope in terms of outcomes – and the non-availability of trial data for some scoped outcomes such as mortality – represents a limitation in terms of clinical inputs to the model. The ERG considered that LEPR and POMC are best considered separately rather than as a pooled population. Clinical advice to the ERG was that while these two populations have some commonalities, the extent of biological and clinical differentiation is sufficient to make it preferable to consider the populations separately.

Table 6: Summary of decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
Population	People with LEPR deficiency obesity or POMC deficiency obesity aged 6 years and over, with the following obesity markers: • people aged 18 and over: body mass index (BMI) 30 kg/m^2 and over; • people aged 17 and under: weight 97th percentile or more for age on growth chart assessment.	N/A	N/A	The ERG noted that the CS scope considered a narrower population than the NICE scope, although the CS itself had not stated this. The CS scope included only biallelic mutations. Clinical advice to the ERG indicated that this would correspond to most severe cases of LEPR or POMC deficiency. However, the NICE scope was broader, and clinical advice indicated that it would include patients with less severe disease, such as heterozygous carriers, as well. This may present a challenge to generalisability.
Intervention	Setmelanotide	Setmelanotide in combination with standard management	Setmelanotide is not expected to replace standard management in treatment of obesity patients with genetic POMC/PCSK1 or LEPR deficiencies, rather it is expected to improve the impact of those interventions after an	The ERG was satisfied that this deviation from scope was reasonable given the intended positioning of setmelanotide as an addition to rather than replacement for standard management. However, it should be

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
			initial weight-loss period following treatment with setmelanotide	noted that the co-administration of setmelanotide with standard management in the company trials complicates the comparison of setmelanotide with the scoped comparator standard management.
Comparator(s)	• Standard management without setmelanotide (including a reduced calorie diet and increased physical activity) • orlistat • methylcellulose • bariatric surgery	Only standard management without setmelanotide has been included as a comparator	KOL opinion is that orlistat and methylcellulose are inappropriate treatments for these patients as they do not treat hyperphagia, the underlying cause of obesity in these patients. Similarly, bariatric surgery does not treat the underlying cause of disease and weight loss is not maintained[29]. In addition, KOL opinion is that it is potentially harmful to reduce stomach size in a patient with untreated hyperphagia	Clinical advice to the ERG indicated that orlistat and methylcellulose would not have sufficient 'horsepower' to be efficacious for LEPR or POMC associated obesity and that bariatric surgery is broadly considered dangerous in this indication. In response to Clarification question A1, the company further explained the mechanistic reasons and clinical expert opinion underlying the decision to exclude these comparators, and also cited a paper[29] demonstrating that initial weight loss in this population following bariatric surgery is

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
				frequently followed by subsequent weight gain. Furthermore, the ERG considered that including bariatric surgery as a relevant comparator in the economic model would not be meaningful due to the fundamental differences between surgical and medical interventions. Overall, the ERG considered the company's exclusion of these comparators to be appropriate.
Outcomes	The outcome measures to be considered include: • BMI • BMI Z-score • weight loss • percentage body fat • waist circumference • hunger	Outcomes include: • BMI • BMI Z-score • Weight loss • Hyperphagia • Obstructive sleep apnoea • Osteoarthritis • NAFLD • Type 2 diabetes • CV events • Mortality	Health related quality of life data for carers are not available and so have not been included in the model. AEs have not been included as no serious treatment related AEs were reported in the clinical trials and none of the AEs reported led to withdrawal or death. Any SAEs reported were not considered related to setmelanotide treatment	The ERG noted that the company scope excluded certain outcomes from the NICE scope. Health-related quality of life for carers was excluded from the company scope. Also, the scope of co-morbidities was narrowed from the NICE scope, and cancer excluded. Data on these outcomes were not collected and could therefore not be

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
	• incidence of type 2 diabetes • cardiovascular events • mortality • co-morbidities associated with early onset severe obesity including cancer • adverse effects of treatment • health-related quality of life (for patients and carers).	• HRQoL (patients)	Cancer was not included as patients' life expectancy of untreated patients was not considered to be long enough to justify inclusion. Hunger scores from the clinical trials were converted to hyperphagia disutilities.	modelled. This represents a limitation. The ERG noted that AEs were not modelled. This may not be appropriate, given that discontinuations were noted in the pivotal studies RM-493-012 and RM-493-015. Furthermore, based on clinician input to the ERG, discontinuation may occur due to burden of administration and AEs, in particular skin pigmentation which may occur as a result of setmelanotide use. With respect to the omission of cancer as a key co-morbidity, the ERG considered that this could have been modelled in the setmelanotide arm, given the life year gain associated with treatment. However it is worth noting that the inclusion of cancer within the model is unlikely to impact on the base case ICER, given that the key drivers of cost effectiveness relate

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
				to the treatment acquisition costs of setmelanotide, as well assumptions surrounding long term treatment effectiveness and HRQoL associated with hyperphagia.
Economic analysis	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used • NHS England future re-organisation of its obesity services • Incorporation of genetic testing as part of clinical practice	The company did not submit a patient access scheme for setmelanotide. The company assumed that the introduction of setmelanotide would not be associated with re-organisation of NHS England obesity services. The company did not consider the cost associated with genetic testing in the economic model.		The company submitted a cost utility analysis and QALYs were used as appropriate. Based on clinician input to the ERG, the introduction of setmelanotide is unlikely to result in significant re-organisation of NHS England obesity services.

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
Subgroups	None stated.	N/A	N/A	The ERG noted that no subgroups had been listed in the NICE final scope. The ERG considered based on clinical advice that LEPR and POMC related obesity should be considered separately. The company provided subgroup analyses results stratified according to whether the patient had POMC or LEPR and whether the patient was adult or paediatric. Results for the following four subgroups were provided by the company and presented in the CS. • LEPR (paediatric) • LEPR (adult) • POMC (paediatric) • POMC (adult)

	Final scope issued by NICE	Variation from scope in the submission	Rationale if different from the final NICE scope	ERG comment
Special considerations including issues related to equity or equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements	N/A	N/A	The ERG did not identify any additional equity or equality considerations.

Abbreviations: AE, adverse events; BMI, body mass index; CS, company submission; CV, cardiovascular; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; KOL, key opinion leader; LEPR, leptin receptor; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; QALY, quality-adjusted life year; SAE, serious adverse events

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence associated with the treatment of people with obesity due to LEPR or POMC/PCSK1 deficiency, as summarised in Table 7. The inclusion criteria were sufficient to capture all relevant evidence for this appraisal, with the single exception being a departure from NICE scope in respect of zygosity of mutations, effectively narrowing population for inclusion.

The methods used to conduct the review were of a good quality, thought the ERG disagreed with certain aspects of quality appraisal; the ERG also considered the lack of independent and duplicate data extraction to increase the risk of biases and errors. The ERG noted that the results of the systematic review search and screening procedures were reported primarily at the publication level, rather than at the study level. For example, in the results presentation, rather than presenting each study in turn, the company initially presented published data, subdividing this by publication rather than by study. Additionally, no summary tables were provided for these published data, which affected the coherence of the CS as a document. Then, the company presented unpublished data, sub-divided by study. This represented a departure from standard systematic review reporting procedures and made it more difficult for the ERG to gain a full and clear picture of the clinical evidence base.

Table 7: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Section C.9.1; Appendix 1.1.1 to 1.1.5	The company carried out literature searches for genetic obesity in a good range of sources. Embase and Medline appear to have been searched together with one strategy, which is not best practice as these databases use different indexing terms and should be searched separately. It is possible that some records could have been missed using this method. The strategy for LEPR/POMC appears thorough; the second part of the strategy (obesity/hyperphagia) is brief and does not include any subject heading terms, it is therefore likely that some records may have been missed. The Cochrane Library search also does not include any subject headings for obesity/hyperphagia.

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Inclusion criteria	Table 8, Section C.9.2; Appendix 1.1.6	The inclusion criteria for the clinical effectiveness review, as specified in Table 8 (CS, p.40), are considered appropriate to the decision problem. The ERG agreed with the company's criteria for including mixed populations with patients of interest as well as patients not of interest, though it again noted the departure from the NICE scope in terms of its restriction to biallelic disruptive mutations. The ERG noted the exclusion of orlistat, methylcellulose and bariatric surgery as specified by NICE scope, but considered these exclusions to be appropriate as highlighted in Table 5.
Screening	Section 9.2; Appendix 1.1.6	Screening was conducted to appropriate standards to minimise selection bias, with duplicate screening and arbitration by a third reviewer at title/abstract and full-text stages.
Data extraction	Section 9.2; Appendix 1.1.7	Data extraction was conducted to appropriate standards to minimise selection bias, with single reviewer extractions checked by a second reviewer and arbitration conducted by a third, if necessary. The ERG noted that data extraction was not done independently and in duplicate, potentially introducing bias or errors. The stated approach to grouping multiple publications reporting on the same study was reasonable, though the ERG noted that the CS departed from this approach by separately reporting study results for published and unpublished sources, and further splitting published evidence to the level of the publication. This has proved challenging in gaining a full, clear picture of the results presented by the company.
Tool for quality assessment of included study or studies	Section 9.2	The single-arm interventional design, with placebo withdrawal period, of the included trials most closely resemble an observational, uncontrolled before-after design (CRD 2008[30]) with a nested placebo-controlled period. As a result, the ERG considered the modified CASP (CASP UK 2021[31]) and Cochrane Risk of Bias (Higgins et al 2011[32]) tools used by the company as appropriate for observational and randomised placebo-controlled components, respectively. However, it is not clear why the Cochrane Risk of Bias tool was used for the long-term extension study RM-493-022 and the ERG considered CASP to be more appropriate in this case. The ERG noted that the first version of the Cochrane Risk of Bias tool was used in assessments - not the Cochrane Risk of Bias 2.0 tool, as stated by the company. As a result, quality appraisal using both tools was conducted at the study level and did not take into account the potential for variation in risk of bias across outcomes. The ERG further noted that the quality appraisals were conducted by one reviewer, and

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		validated by a second, though no details are provided on interrater agreement or arbitration of conflicts.
Evidence synthesis	Section 9.8	The findings of the included studies were presented without evidence synthesis. The company indicated that this was not feasible given the lack of effectiveness data for standard of care as a comparator. The ERG considered this rationale reasonable, as clinical advice to the ERG indicated diet and exercise to be ineffective in managing the weight of people with LEPR or POMC deficiency; making the existence of studies describing its effectiveness unlikely.

Abbreviations: CASP, Critical Appraisal Skills Programme; CRD, Centre for Reviews and Dissemination; CS, company submission; ERG, Evidence Review Group; LEPR, leptin receptor; NICE, National Institute for Health and Care Excellence; POMC, proopiomelanocortin

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review[33-35]

The CS describes four trials of setmelanotide for LEPR or POMC-based obesity. These comprise one single arm study (RM-493-011), one open-label extension study (RM-493-022) and two open-label trials with placebo-controlled withdrawal periods (RM-493-012 and RM-493-015) (Table 8). Trials RM-493-012 and RM-493-015 are identically designed and differ only by population criteria. The ERG noted that clinical effectiveness results were presented by publication, rather than by study, which presented an unnecessary complication, and deviated from standard systematic review reporting procedures. Moreover, the ERG noted that results for some relevant outcomes were only reported in the clinical study reports (CSRs) or study publications and not in the CS or its appendices. The presentation of results in the CS was focused on the primary and secondary outcomes of the trials, rather than being focused on the NICE scope and decision problem. This was detrimental to the clarity of the presentation of the evidence in the CS.

Table 8: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
RM-493-011	Single-arm study	Obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway, POMC-homozygous, heterozygous, and epigenetic deficiency, or LEPR deficiency.	Setmelanotide starting at optimal individualized dose escalating to a maximum of 2.5 mg per day.	None	Interventional – clinical trial
RM-493-012	Open-label with an 8 week double-blind placebo controlled withdrawal period	POMC deficiency obesity due to biallelic, loss-of-function POMC or PCSK1 gene mutations.	Setmelanotide once daily with a starting dose of 1.0 mg for adults and 0.5 mg for paediatric patients (0.25 mg in paediatric patients in Germany and France), titrated upwards in 0.5 mg increments to a maximum of 3.0 mg (2.5 mg in Germany and France, and in paediatric patients).	Placebo	Interventional – clinical trial
RM-493-015	Open-label with an 8 week double-blind placebo controlled withdrawal period.	Biallelic, homozygous or compound heterozygous (a different mutation on each allele) status for either LEPR gene, with the loss-of-function variant for each allele conferring	Setmelanotide once daily with a starting dose of 1.0 mg for adults and 0.5 mg for paediatric patients (0.25 mg for paediatric patients in Germany), titrated upwards in 0.5 mg increments to a	Placebo	Interventional – clinical trial

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
		a severe obesity phenotype. 11 pivotal participants, 4 supplementary participants.	maximum of 3.0 mg Maximum doses in for paediatric patients globally, as well as for adult patients in Germany and France were set at 2.5 mg, though France re-adjusted the maximum dose for adults to 3.0 mg after one year.		
RM-493-022	Open-label extension trial	Patients who have completed a trial of setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4R in the leptin-melanocortin pathway.	Setmelanotide at the finishing dose from the previous trial, up to a maximum of 3.0 mg, or 2.5 mg in Germany.	None	Interventional – clinical trial

Abbreviations: CS, company submission; LEPR, leptin-receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase-subtilisin/kexin type-1; POMC, proopiomelanocortin; RCT, randomised controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design and conduct of the studies

RM-493-011 is a single-arm (setmelanotide in combination with standard management – no comparator arm) trial described by two publications: Kühnen et al 2016[33] included people with obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway; Clément et al 2018[34] included people with POMC-homozygous, heterozygous, and epigenetic deficiency, or LEPR deficiency. It is the earliest and smallest included trial in the CS. The company did not include RM-493-011 in the economic model for this appraisal due to the small sample size and this trial being superseded by the phase 3 trials. The ERG considered this exclusion to be appropriate.

RM-493-012 and RM-493-015 are phase 3 trials with an open-label treatment period and a double-blind, variably timed, placebo-controlled withdrawal period lasting eight weeks. The trial design was identical except for the obesity genotypes these included, with RM-493-012 including participants with LEPR deficiency and RM-493-015 including participants with POMC deficiency. The publication by Clément et al 2020[35] reports on the results of both trials, with included participants referred to as the 'pivotal' cohorts, while separate CSRs reported on unpublished data from 'supplemental' cohorts that were generated following publication.

Trial RM-493-012 was conducted internationally with sites in the United States, France, Germany, Canada, Spain, and Belgium. The trial was split into a pivotal cohort 10/15 (66.67%), where 1/10 (10%) patient was from United States, 1/10 (10%) from France, 7/10 (70%) were from Germany and 1/10 (10%) was from Canada. In the supplemental cohort, 1/5 (20%) patient was from France, 2/5 (40%) were from Spain and 2/5 (40%) were from Belgium. Four patients had POMC biallelic mutations; one had PCSK1 biallelic mutation. Several impactful protocol amendments were made, including a change in the minimum starting dose for paediatric patients aged six to 11 years, and a maximum dose of 2.5 mg in France and Germany, as well as a maximum paediatric dose of 2.5 mg for patients in the USA and UK as requested by the Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA). In a later amendment the possibility of a dose reduction once the patient had reached a long-term target was considered which would have impact on the cost of the technology, the real-world use and potential long term-efficacy outcomes of setmelanotide.

RM-493-015 was also conducted internationally and was a parallel trial to RM-493-012, and had sites in the UK, the Netherlands, Germany and France. Patients were also split into the pivotal

cohort (11), where 4/11 (36%) were enrolled in France, 3/11(27%) in Germany, 3/11 (27%) in the Netherlands and 1/11 (9%) in the UK. This trial is the only of the four to include a UK patient. There were four participants in the supplemental cohort, 2/4 (50%) from France, and 1/4 (25%) from Germany and 1/4 (25%) from Canada. The ERG noted the substantive protocol amendments made throughout the trial, and that the small patient population size with a change in maximum dose in some countries adds significantly to the uncertainty in the trial. Amendments 1 and 2 details regulatory rulings in France and Germany leading to changes in the trial dosing regimen, temporarily in France and permanently in Germany.

Trial RM-493-022 is a long-term extension trial of setmelanotide for patients who have completed a trial of setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. All seven (100%) participants included in the CSR had obesity due to POMC/PCSK1 mutations and were from Germany. The ERG noted that six participants with LEPR deficiency obesity were included in the original report rider dated 30 April 2020.

It remains unclear to the ERG which trials were used in the economic model. The CS stated that RM-493-011 was excluded from the model. The model file shows that BMI clinical effectiveness inputs came from trials RM-493-012 and RM-493-015 only. However, regarding initial setmelanotide response rates, it is only stated that the data come from the 'setmelanotide CSR' without specifying which trial. Data from RM-493-022 were not used in the economic model (see Section 4.2.6.1); the ERG questioned the appropriateness of this exclusion.

German participants in all trials were capped at a dose of 2.5 mg, which the ERG considered to be likely to have implications on generalisability (See Section 3.2.2.3).

3.2.2.2. Population

Trial RM-493-011 considered participants with obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway as well as participants with POMC-homozygous, heterozygous, and epigenetic deficiency, or LEPR deficiency. The ERG considered this to represent a fairly broad population.

Trial RM-493-012 considered a population of POMC deficiency obesity due to biallelic, loss-of-function POMC or PCSK1 gene mutations, whereas the population considered in trial RM-493-15 were those with a biallelic, homozygous or compound heterozygous, loss-of-function LEPR gene mutation. The ERG considered this to be within the scope, but fairly narrow, only

addressing a subset of patients eligible under the NICE scope for this appraisal. However, it should be noted that trials RM-493-012 and RM-493-015 are identical trials except for addressing different sub-populations within the NICE scope, and when both considered together cover the scoped population. The ERG considered it to be appropriate that the different mutations were in separate trials, after clinicians advised of the heterogenous nature of the different gene mutations.

For trial both RM-493-012 and RM-493-015, the ERG considered the exclusion criteria to be comprehensive, and therefore the number of patients included in the trial was limited. The exclusion criteria, detailed in Table 12 in the company submission (Doc B, CS), highlighted those who have had successful gastric bypass surgery, lost or maintained weight through diet and exercise recently, scored 15 or more on the Patient Health Questionnaire-9 (PHQ-9), or have any severe suicidal ideation were all excluded. Considering the nature of the condition, patients who are likely to benefit from setmelanotide were excluded from the trial. In addition, the ERG raises questions over the generalisability of the trial to the UK population of patients with LEPR-deficiency, as many patients are likely to meet one or more of the exclusion criteria of the trial.

The extension trial, RM-493-022 had an equally comprehensive set of exclusion criteria, with the exception of not excluding patients who have successfully lost weight through diet and exercise, or who have recently had successful gastric band surgery, which slightly increased the pool of patients to be recruited, but it is still narrow. Additionally, patients in RM-493-022 were required to have participated in a previous trial of setmelanotide treatment.

3.2.2.3. Intervention

The intervention for the four trials was setmelanotide in combination with standard management. The ERG considered the dose titration method used in the non-pivotal trial RM-493-011 to be appropriate.

In trial RM-493-015, patients were treated with setmelanotide according to its licensed dose. Patients initially were given a SC injection once daily in the morning, starting with 1.0 mg in adults, 0.5 mg in adolescent and paediatric patients; apart from Germany, where the starting paediatric dose was 0.25 mg. The dose was titrated upwards approximately 0.5 mg every two weeks for up to 10 weeks, according to protocol and the patients' tolerability, up to a maximum of 3.0 mg, except where local licensing variations precluded this as discussed below. In Germany and France, the maximum dose was limited to 2.5 mg. A later amendment in France

restored the maximum dose of 3.0 mg. This raises issues over the generalisability of the trial, and the uncertainty of the long-term efficacy and safety of a 3.0 mg dose, especially considering that setmelanotide is anticipated to be prescribed for the duration of the patient's life. [redacted] Furthermore, all POMC/PCSK1 patients were from Germany, meaning that none received the 3.0 mg dose, which the ERG considered to be a concern in terms of generalisability.

In the extension trial RM-493-022, patients were administered open-label setmelanotide by SC injection once daily each morning and continued on the same dose that was administered at the end of the index study, though the ERG highlighted previously that the maximum dose was limited to 2.5 mg, as all 7 participants in the trial were from Germany. Amendment 1 to the extension trial included a decrease in the maximum time on the study treatment, which considering the vast uncertainties throughout the trials from the small patient numbers, and the short follow-up time during the initial trials, seems counterintuitive. Across the included trials, German participants were capped at 2.5 mg by regulatory authorities. The ERG noted that the proposed UK dose could not be used in the extension trial that provides the greatest follow-up data to inform this appraisal. This substantially limits the effectiveness and safety data for setmelanotide available for the 3.0 mg dose.

3.2.2.4. Comparator

Due to the small patient population, and subsequently the low number of patients in the RM-493-012 and RM-493-015 trials, they include an eight-week, double blind, placebo-controlled withdrawal sequence, so patients serve as their own control. The patients received placebo for four weeks, and the study treatment for four weeks, during this period. The placebo treatment for this trial was 'vehicle', i.e. the treatment without setmelanotide as the active ingredient; though the substance was not reported.

In the extension trial RM-493-022, the patients were administered open-label setmelanotide, with no comparator group. The earliest trial in the series RM-493-011 also did not include a comparison group.

3.2.2.5. Outcomes

The outcomes reported in the four trials are summarised in Table 9 below.

The primary outcome of trial RM-493-011 was percent change in body weight and BMI from baseline. While a series of anthropometric, hunger, biochemical, developmental and safety outcomes were included, the full range of outcomes in the NICE scope was not covered.

The primary outcome of trials RM-493-012 and RM-493-015 was at least a 10% weight reduction at approximately one year compared to baseline. This outcome was measured in the full analysis set (FAS), which included all patients who received any active study treatment and had at least one baseline assessment. Key secondary endpoints included the percentage change in body weight and 'most hunger in the past 24-hours', measured in the designated use set (DUS) population, which included all patients who received any active study treatment, demonstrated ≥ 5 kg or 5% loss of initial body weight over the 12-week open-label treatment and proceeded into the double-blind, placebo-controlled withdrawal period. A categorical analysis for a threshold of ≥25% improvement in hunger scores was also analyzed in the DUS population. Not all scoped outcomes were measured in the trial: there were no data for cardiovascular events, mortality, or cancer related co-morbidities; the latter was also not reported in the company scope. Additionally, although the trial reports glucose parameters, the follow-up period is not long enough to measure the incidence of type 2 diabetes. Among the outcomes in the scope that the trial did measure, there was also heterogeneity in the way outcomes were measured, for example, BMI and BMI Z-score were not directly reported in the trial outcomes. Health-related quality of life (HRQoL) for both patients and carers was in the NICE scope, whereas only patient health-related quality of life was included as an outcome in the trial, and carer health-related quality of life was not in the company scope.

The primary objective of the extension study RM-493-022 is to assess the safety and tolerability of setmelanotide in patients who have completed treatment in a previous trial. The ERG noted that not all NICE scoped outcomes are included in this trial either, i.e. mortality, incidence or co-morbidities related to cancer.

The ERG noted that none of the included trials provided data on four of the NICE scoped outcomes: HRQoL for carers, cardiovascular events, co-morbidities and mortality. HRQoL was excluded from the company scope and the company narrowed the scope of co-morbidities compared to the NICE scope. Cardiovascular events and mortality remained in the company scope, but no data were provided. The ERG considered the lack of data on HRQoL for carers, which was excluded from the company scope, to preclude a full perspective on the psychosocial implications of LEPR and POMC associated obesity. Moreover, the lack of data on mortality and

cardiovascular events in any of the included trials represented an important area of uncertainty, given the expected shortened life expectancy and worse co-morbidity profile in LEPR and POMC associated obesity. In RM-493-022, with the follow-up period reduced from five years to two years, the level of uncertainty was further increased.

BMI and BMI Z-score

All included studies included a BMI measure, typically mean change in BMI. One trial (RM-493-011) did not additionally consider BMI Z-scores as none of the participants were younger than 18 years, which is a limitation in a paediatric population. This trial was not, however, included in the economic model and is therefore not a key concern for this appraisal.

Weight loss

Trial RM-493-011 considered weight loss conceptualised in terms of mean percentage change in body weight.

In trials RM-493-012 and RM-493-015, the primary endpoint for determining clinical efficiency of setmelanotide was the proportion of patients reaching the ≥ 10% weight loss threshold after approximately one year. The company outlined the success criteria whereby success was defined as 35% of the sample reaching the ≥ 10% weight loss threshold. In trial RM-493-015, the ERG noted that the power calculation for a 95% ($p<0.05$) confidence in the clinical effects of setmelanotide was 50% of patients losing ≥10% of their body weight. Considering this not to be met, the company accepted a more liberal significance threshold of 90% ($p<0.1$) confidence. However, as presented in the results (Section 3.2.3.2), in RM-493-015, the 50% threshold required in the power calculation was met when both pivotal and supplementary patients from the FAS were considered. Therefore, the ERG had concerns about the appropriateness of deviating from the customary 95% ($p<0.05$) threshold. The ERG furthermore considered 35% to be a low success threshold, which adds to the uncertainty regarding the clinical effectiveness of setmelanotide in the context of a small patient population.

A secondary endpoint relating to the NICE scoped outcome of weight loss was the mean percent change in body weight from baseline, which was measured in the DUS population. The ERG considered this an appropriate method of outcome measurement but considered that some trial participants were paediatric or adolescent and still gaining weight naturally. As a result, the ERG noted that the decrease in mean weight in RM-493-015 from 131.7 kg at baseline to 115.0 kg at approximately one year may be an underestimation of the fat loss

experienced, and would consider fat loss, rather than weight loss, to be a more appropriate measure.

In the extension trial, RM-493-022, weight loss was measured when patients were in a fasted state in each visit, as well as measured monthly between visits by the parent or caregiver for paediatric patients.

Percentage body fat

Body fat, which was measured both in grams and percentage lost was a secondary outcome of all four included trials. This was measured using dual-energy x-ray absorptiometry (DEXA) scans and bioelectrical impedance (BIA). In RM-493-015, the ERG noted that only six patients in the pivotal cohort and three patients in the supplemental cohort had their body composition assessed at baseline. At approximately one year, only five patients had body mass and body fat measured in the pivotal cohort, and no patients from the supplemental cohort had body fat and body mass measured at approximately one year. Although significant decreases from baseline in body fat and body mass were seen at follow-up in those patients who were measured on both occasions, the small patient population adds significantly to the uncertainty of the clinical efficacy of setmelanotide.

Waist circumference

In trials RM-493-012 and RM-493-015, all pivotal patients had waist circumference measured at baseline, according to US National Heart Lung and Blood Institute criteria, and six patients had waist circumference measured at 52 weeks follow-up. The method of waist circumference measurement was continued in the extension trial RM-493-022. Waist circumference measures are not provided in trial RM-493-011.

Hunger

There were three variations of hunger scores collected throughout the RM-493-012 and RM-493-015 trials, ‘morning hunger’, ‘worst hunger in 24 hours’, and ‘average hunger in 24 hours’, measured in patients 12 years and older. The ERG considered the varied measurement of the hunger scores to be appropriate and comprehensive.

There was a lack of detail around the hunger outcome in trial RM-493-022, where questions were asked in accordance with Global Hunger Questions. For patients aged six to 11 years, the parent or carer answered these on the patients’ behalf. The ERG questioned the reliability of

this patient- or observer-reported outcome, especially in an unblinded trial, as it could lead to bias in favour of the study treatment. Hunger scores from trial RM-493-011 were reported using an 11-point Likert scale.

The CS and subsequent clarification response from the company did not explain to the ERG's satisfaction how hunger scores were mapped to hyperphagia disutilities in the economic model (see Section 4.2.6.5).

Incidence of type 2 diabetes

The ERG noted that incidence of type 2 diabetes was not directly observed in any of the included trials, due to short follow-up periods and the low patient population. However, glucose parameters, which are a marker of diabetes, were reported.

Oral glucose tolerance testing (OGTT) was performed to evaluate the effects of setmelanotide on postprandial glucose and insulin in trials RM-093-012 and RM-093-015, however, a baseline OGTT was not performed for subjects with a diagnosis of type 1 or type 2 diabetes, additionally adding the uncertainty of setmelanotide in reducing blood sugar levels for those patients with diabetes.

In trials, RM-493-012 and RM-493,015, glucose parameters as measured by fasting glucose haemoglobin A1c (HbA1c) and OGTT with a focus on insulin sensitivity over time were assessed, which may be used to estimate future incidence of diabetes, although the ERG highlighted that there is considerable uncertainty associated with this approach.

In the extension trial RM-493-022, fasting glucose and HbA1c parameters were reported.

No measurement of glucose parameters was reported in trial RM-493-011.

Cardiovascular events

The NICE scoped outcome of cardiovascular events was included in the company scope but was not reported in any of the included trials. The follow-up period in the trials was likely too short to detect cardiovascular events such as myocardial infarctions and strokes. The ERG considered this to be a limitation of the available data.

Mortality

The NICE scoped outcome of mortality was included in the company scope but not reported in any of the included trials. The ERG considered that the follow-up period in the trials was also likely too short to detect mortality outcomes. The ERG considered this to be a limitation of the available data. The lack of mortality data represents is an area of great uncertainty. With regard to the extension trail RM-493-022, the ERG noted the shortened follow-up period, which was still relatively short at two years, adding to the uncertainty around changes in mortality when on the study treatment. Clinical advice to the ERG was that POMC and LEPR associated obesity patients would have reduced life expectancy compared to both the general population and people with general obesity, and that this effect would be expected to be greater for POMC than LEPR due to an expected worse co-morbidity profile.

Co-morbidities associated with early onset severe obesity including cancer

The NICE scoped outcome of co-morbidities was narrowed in the company scope to only particular types of co-morbidity, and cancer was excluded. No included trials reported co-morbidities as an outcome. However, for example, trial RM-493-015 reported several co-morbidities, measured at baseline for patients. Trial follow-up periods were likely insufficient to capture co-morbidity outcomes. The absence of these outcomes, including on cancer incidence, adds to the uncertainty in the clinical evidence. The ERG considered this an important unreported area due to the common complications associated with the disease. Indeed, clinical advice to the ERG highlighted that those patients with POMC deficiency are likely to have a lower life expectancy than patients with LEPR deficiency – with both having a lower life expectancy than the general population and people with general obesity, with higher BMI and more obesity-associated co-morbidities playing an important role.

Adverse effects of treatment

All adverse events, treatment-emergent adverse events, withdrawals and fatalities were collected across all reported trials. The ERG noticed certain discrepancies in the reporting of adverse events in the originally supplied CS (see Section 3.2.3.2).

Health-related quality of life (for patients and carers)

In trials RM-493-012 and RM-493-015 for adult patients, HRQoL was assessed using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the self-reported instrument SF-36

was used to measure functional health and well-being. For patients <18, health related quality of life was assessed with the validated Paediatric Quality of Life Inventory (PedsQL) and the 10-Item Health Survey for Children (SF-10) for patient self-report and caregiver-reported assessment. The ERG considered these appropriate measures, but highlights that the HRQoL was not reported for carers. Indeed, HRQoL for carers was excluded from the company scope. This precluded a full perspective on the psychological impact of POMC and LEPR deficiency-associated obesity.

In RM-493-022, only baseline HRQoL data are available, as it is the endpoint for the index studies, but no further measurements have been taken throughout the extension trial. The ERG noted that the lack of data on this adds to the ongoing clinical uncertainty around the clinical benefits of setmelanotide.

The CS did not contain any information regarding how HRQoL was measured in trial RM-493-011.

Table 9: Clinical efficacy outcomes reported across the included trials

Outcome	RM-493-011	RM-493-012	RM-493-015	RM-493-022
BMI	✓	✓	✓	✓
BMI Z-score	x	✓	✓	✓
Mean percentage change in body weight	✓	✓	✓	✓
Proportion of participants achieving ≥10% weight loss from baseline to approximately one year	x	✓	✓	x
Percentage of participants with 5%, 10% 15%, 20%, 25%, 30%, 25% and 40% weight loss from baseline	x	✓	✓	x
Change in waist circumference	✓	✓	✓	✓
Mean percentage change in 'most hunger' score in participants ≥12 years	x	✓	✓	x
Percentage of participants who achieved ≥25% reduction in 'most hunger' score	x	✓	✓	x
Hunger score	✓	X	X	✓
Hunger in patients age 6 to 11 years	x	✓	✓	✓
Reversal of weight loss and hunger reduction during the placebo controlled withdrawal sequence	x	✓	✓	x
Glucose parameters: fasting glucose, HbA1c, and OGTT with a focus on parameters of insulin sensitivity	x	✓	✓	✓
Change from baseline in resting energy expenditure	✓	✓	✓	x
Percentage change in body fat mass	✓	✓	✓	✓
Percent change in total body mass, non-bone lean mass, and bone density.	✓[a]	X	X	✓
Cardiovascular parameters: heart rate and blood pressure (DBP and SBP)	✓	✓	✓	✓
Fasting lipid panel (TC, HDL-C, LDL-C and TG)	✓	✓	✓	✓

Outcome	RM-493-011	RM-493-012	RM-493-015	RM-493-022
Change in hs-CRP	x	✓	✓	✓
Change in quality of life and health status	x	✓	✓	✓
Changes in neurocognition in patients aged six to 16 years	x	✓	✓	✓
Change in pubertal development for patients yet to reach Tanner Staging V	x	✓	✓	x
Change in growth and development assessed by bone age	x	✓	✓	✓
Safety and tolerability of setmelanotide	x	✓	✓	✓
Skin pigmentation	x	✓	✓	✓
Hormonal, neuroendocrine, metabolic and anti-inflammatory analytes and biomarker assays	✓	✓	✓	✓
Liver and kidney parameters: ALT, AST, bilirubin, creatinine	✓	✓	✓	✓
Pharmacokinetic/pharmacodynamic parameters	✓	✓	✓	✓

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; OGTT, oral glucose tolerance test; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides

[a] lean body mass only

3.2.2.6. Critical appraisal of the design of the studies

The company's approach to the critical appraisal of included trials was reported in the CS (Section 9.2, p.42). The critical appraisal of published evidence, i.e. results from the pivotal cohorts for RM-493-012 and RM-493-015 (Clément et al 2020[35]) as well as from two studies reporting on RM-493-011 (Kühnen et al 2016[33]; Clément et al 2018[34]), using a modified CASP tool was reported in Section 9.5.1.1 (p.77-78 of the CS). The critical appraisal of unpublished studies, i.e. results from RM-493-012 and RM-493-015 (Clément et al 2020) as well as from the long-term extension trial RM-493-022 (Rhythm CSR[36], CS reference 56), using the Cochrane Risk of Bias tool was reported in Section 9.5.1.2 (p.78-81 of the CS).

As the noted in Table 7, the ERG considered CASP to be appropriate for the observational before-after aspects of the four studies, and Cochrane Risk of Bias broadly appropriate for the placebo-controlled withdrawal periods of RM-493-012 and RM-493-015. It was not clear from the company submission why CASP was applied to published studies and Cochrane Risk of Bias to unpublished studies; in particular, the ERG did not consider the latter to be appropriate for RM-493-022. A modified CASP assessment for this trial was completed by the ERG.

RM-493-011

The ERG considered the judgments made by the company to be mostly appropriate. With regards to the first domain of the modified CASP tool, relating to whether the cohort was recruited in an acceptable way, the ERG considered 'Can't tell' or 'Not clear' a more appropriate response than 'Yes'. This was due to a lack of specific information on how the two patients described in Kühnen et al 2016[33] and three patients described in Clément et al 2018[34] were recruited. By the company's own reckoning, opportunistic sampling caused some concern, though the company described this as the only feasible method of recruitment. Furthermore, the ERG considered these sample sizes too small to render findings fully generalisable. Though exposure differed due to individualised therapeutic doses, the ERG considered the judgment presented by the company, that bias due to differences in exposure measurement was minimal, to be reasonable; particularly in the light of intended exclusions due to non-adherence. The ERG accepted that anthropometric approaches to determining body weight are highly established and fairly standardised, but could not find explicit description of such methods and considered 'Can't tell' or 'Not clear' to be a more appropriate response to the domain describing the measurement of the outcome. The ERG noted that follow-up of participants in the studies

was complete but was likely not long enough to detect any long-term adverse events due to maximal follow-up of 61 weeks.

RM-493-012 and RM-493-015

The ERG considered the judgments the company made, using the modified CASP tool, to be broadly appropriate for the two studies. The ERG noted that the publication by Clément et al 2020[35] did identify the presence of confounding co-morbidities in one participant with POMC deficiency, but agreed with the company that this was not comprehensive enough to conclude that all important confounders were identified. The ERG noted that follow-up of participants in the pivotal studies was complete, with one and four non-responders excluded for POMC and LEPR deficiency, respectively. Follow-up was complete in the supplemental cohort for RM-493-015, but less complete for the supplemental cohort of RM-493-012, with two if the five additional participants withdrawn from this study. The ERG considered follow-up as likely not long enough to detect any long-term adverse events due to follow-up of approximately 52 weeks, involving 48 weeks of interrupted exposure to setmelanotide.

With regards to the assessment done using the Cochrane Risk of Bias tool, it was not clear whether this assessment applied only to the placebo-controlled withdrawal period of the studies; given references to longer time points at approximately one year. Therefore, the ERG did not consider the application of the tool wholly appropriate. The ERG disagreed with the company's assessment of allocation concealment. The concealment of allocation was not described in Clément et al 2020, and the rationale for the judgment in Table 24 of the CS (p.78) relates to blinding rather than allocation concealment.

As the Cochrane Risk of Bias 2 tool was not used, bias was not assessed at the outcome level. This predominantly affects the assessment of the appropriateness of the analysis method. Thought the ERG agrees that an appropriate modified intention-to-treat analysis was conducted for the primary endpoint, using the full analysis set, it is not clear what the approaches were for all other outcomes. Approaches mentioned, such as baseline observation carried forward or last observation carried forward, are not considered robust methods of imputation. The ERG agreed with the company's assessment that there was no evidence of selective outcome reporting, however, no other domains could be judged or appraised due to the limitations imposed by the study designs.

As the placebo-controlled withdrawal period, and subsequent restarting of setmelanotide, most closely resembles a cross-over trial design, the ERG felt that domains associated with the design should have been assessed. The ERG considered the studies to be at low risk of bias from period effects (Dwan et al 2019[37]), given the nature of the condition, and also did not find any evidence of selective first-period reporting (Freeman 1989[38]). The risk of bias due to carry over effects was considered to be unclear by the ERG, as the study publication did not report testing for clearance of setmelanotide. The ERG acknowledged that this uncertainty would bias results in a conservative direction, potentially favouring the placebo period, and also also recognised the benchmark for continuation into the placebo-controlled withdrawal phase matches the stopping rule highlighted by the company.

RM-493-022

As discussed in Section 3.1, the ERG did not consider the assessment of this study with the Cochrane Risk of Bias tool to be appropriate, given the study design. The ERG completed the modified CASP assessment, as used in the other included studies for this study in Table 10 below.

Table 10 Critical appraisal of RM-493-022 conducted by the ERG

Study question	RM-493-022
Was the cohort recruited in an acceptable way?	Yes. All participants who completed a prior study of setmelanotide were eligible for inclusion.
Was exposure accurately measured to minimise bias?	Yes. Individualised therapeutic doses are reported in the CSR (Rhythm CSR, CS reference 56) and patients could be excluded for non-adherence
Was the outcome accurately measured to minimise bias?	Not clear. Anthropometric approaches to determining body weight are highly established and fairly standardised, but the specific approach was not detailed in the CSR.
Did the authors identify all important confounding factors?	Not clear. Compliance issues were identified as confounders for some participants but is not considered comprehensive enough to conclude that all important confounders were identified.
Did the authors take account of confounding factors in the design and/or analysis?	No. Confounding factors were not comprehensively identified or considered in the design or analysis.
Was follow-up of patients complete?	Not clear. In Table 13 of the CS (p.58-61), the company indicates in different sections that 15 and 16 participants were included. The company reported in Section 9.4.6.2 of the CS (p.76) that no patients were reported as discontinuing. Under the section detailing follow-up, it is reported that seven of the nine patients

	included from RM-493-012 provided data in the CSR, none from the ongoing study RM-493-014 provided data at the time of submission. Follow-up of mean 101 weeks (ranging from 75 to 116 weeks) was still considered too short to identify long-term adverse events.
Are the results precise (e.g. in terms of CI and p-values)?	Yes. Clinically significant weight loss is reported in the CSR, and Table 7 in the CSR indicates a mean change in weight of approximately 35 kg with 95% CI showing very little overlap.

Abbreviations: CS, company submission; CSR, clinical study report; ERG, Evidence Review Group

3.2.3. Description and critique of the results of the studies

3.2.3.1. Baseline characteristics

A summary of the baseline characteristics has been reported in Table 11.

The ERG noted the small patient numbers and the resulting uncertainty around the generalisability to the UK and NHS population. Baseline characteristics for the four trials were provided by the company in the CSRs. Due to the placebo-controlled withdrawal period, the trials were single arm and patients acted as their own control.

The ERG were unclear regarding the extent to which baseline characteristics represented in the trial generalised to the target NHS population. In trial RM-493-022, all patients were from Germany, and while the general populations of the UK and Germany are comparable, the trial maximum dose was 2.5 mg due to regulations. The present characteristics were on the SAS set, which were the population who received one dose and at least one post-dose safety assessment. One patient in trial RM-493-015 was under the age of 12 years and in the extension trial, the youngest patient was [redacted] years old, adding to the uncertainty of paediatric efficacy and safety. Additionally, the extension trial only contained patients with the POMC/PCSK1 from the RM-0493-012 trial. The clinical experts highlight the heterogeneity between POMC/PCSK1 and LEPR patients, and that POMC/PCSK1 patients are likely to have a higher BMI and a lower life expectancy than LEPR patients partly due to the presence of more co-morbidities in patients with POMC/PCSK1 deficiencies. Only including POMC/PCSK1 patients in the extension trial may therefore show an overestimate of the results of setmelanotide, especially considering the clinical expert suggested different clinical efficacy results for the two groups of patients.

Table 11: Baseline Characteristics

	[redacted]	RM-493-012[a]	RM-493-015[a]	RM-493-022[a]
Population (n)	[redacted]	15 (10 pivotal and 5 supplemental)	15 (11 pivotal and 4 supplemental	7
Nationality	[redacted]	United States (1) France (2) Germany (7) Canada (1) Spain (2) Belgium (2)	UK (1) France (6) Germany (4) Netherlands (3) Canada (1)	Germany (7)
Age, mean (SD)	[redacted]	17.20 (7.02)	21.67 (8.52)	18.1 (4.10)
Sex	[redacted]	40% female	60% female	42.9% female
Deficiency	[redacted]	POMC (13) PCSK1 (2)	LEPR	POMC/PSK1
Weight (kg), mean (SD)	[redacted]	111.26 (35.81)	132.46 (39.28)	91.56 (17.895)
Height (cm), mean (SD)	[redacted]	[redacted]	[redacted]	176.79 (10.700)
BMI, mean (SD)	[redacted]	39.17 (8.21)	[redacted]	29.60 (7.468)
Waist circumference, mean (SD)	[redacted]	118.09 (62)	128.49 (24.15)	105.29
Morning Hunger Score, mean	[redacted]	[redacted]	[redacted]	NR
Most Hunger Score	NR	NR	7.0 (0.77)	6.43 (2.637)
Body fat (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: LEPR, leptin-receptor; NR, not reported; PCSK1, proprotein convertase-subtilisin/kexin type-1; POMC, proopiomelanocortin; SD, standard deviation

[a] This information is cited from the CSRs and is hence AIC. Some of the information is shown in the CS unmarked, and is reported as such in the ERG report where appropriate.

[b] Information obtained from clinical trial appendices, listing 16.2.1.7. Body fat mean was not presented, and therefore this is an ERG calculation from available data of n=12 patients in FAS set.

3.2.3.2. Clinical effectiveness results

Trial RM-493-011 included seven patients, although outcomes were reported for only five patients: two patients with POMC associated obesity[33] and three patients with LEPR associated obesity[34].

Trial RM-493-012[35] included 10 patients in the pivotal cohort and 5 patients in the supplemental cohort, giving a total of 15 patients. All patients in this trial had POMC/PCSK1 associated obesity. The company's results presentation states POMC – it is unclear if this was a notational simplification or if PCSK1 patients were excluded from the presented analysis.

Trial RM-493-015[35] included 11 patients in the pivotal cohort and four patients in the supplemental cohort, giving a total of 15 patients. All patients in this trial had LEPR deficiency obesity.

Trial RM-493-022 is unpublished. Data were reported for seven patients with POMC/ PCSK1 deficiency obesity.

The number of patients included in the analysis for some trials varied slightly between outcomes. Company reporting of results lacked clarity in this respect. The reporting of results was not ordered to match and align to the order of outcome measures in the decision problem. Moreover, the company, in many data tables in the CS, confusingly used the vague term 'average' in combination with SD to refer most likely to the arithmetic mean (which is the assumption the ERG made), while the only term in the tables that used the precise term 'mean' being 'LS mean', which is not the arithmetic mean but rather the marginal mean. This confusing reporting added to the complexity of appraising the clinical evidence.

BMI and BMI Z-score

In trial RM-493-011, the mean (SD) reduction in BMI was 7.73 (0.75) kg/m^2 for POMC patients and 3.59 (1.82) kg/m^2 for LEPR patients. BMI Z-scores were not reported for this trial.

In trial RM-493-012, an overall mean BMI decrease of 27.8% ($p<0.0001$) was observed for patients in the pivotal DUS cohort, transitioning them from 'severe obesity' to 'overweight' BMI category. When the results from the supplemental cohort were included, the overall mean BMI [redacted]. The baseline mean (SD) BMI Z-score for paediatric patients was [redacted]

In trial RM-493-015, there was a statistically significant decrease in BMI scores [redacted]. The baseline BMI in RM-493-015 was [redacted] The baseline mean (SD) BMI Z-score for paediatric patients was [redacted] (CS, Figure 16, p.117). The information on BMI for trial RM-493-015 was obtained from the CSR, but after the ERG request, more information was provided in table 14.2.1.2.7-D of the CSR Appendix.

More detail on BMI was provided for trial RM-493-022. At baseline [redacted] However, at week 25, BMI was only measured on five patients rather than the seven patients in the trial, and no explanation has been offered for this. Therefore, the ERG highlighted the uncertainty around the increase in BMI, as it is not clear whether this is attributable to the two patients who did not contribute data, or if the impacts of setmelanotide decreased during the extension study period.

Weight Loss

In trial RM-493-011, weight loss from baseline to the end of the main study (12 or 13 weeks) was 16.6% in patient 1 and 13.4% in Patient 2, in the POMC population[33]. Further unpublished data show weight loss in these participants of [redacted] kg and [redacted] kg after [redacted] and [redacted] weeks, respectively. The company reported [redacted] of this weight loss over an additional [redacted] and [redacted] years; however, the ERG noted an increase in weight in patient [redacted] as shown in Figure 10 of the CS. In the LEPR population, as shown in Figure 1 in Clement et al[34], patients lost weight on setmelanotide and gained weight during off-drug periods. The company also reported [redacted] of setmelanotide up to [redacted] weeks for participants with LEPR deficiency obesity.

In trial RM-493-012, 8/10 participants in the pivotal cohort in the FAS population achieved the primary endpoint of ≥ 10% weight loss (90% CI 49.31,96.32, p<0.0001). These results were confirmed by the supplemental cohort, with 12/14 patients in the total population achieving this primary endpoint (90% CI 61.46, 97.40, p<0.0001). At the data cut-off, 7/10 patients in the pivotal cohort had achieved 25% weight loss.

The mean percent change in body weight from baseline to approximately one year of treatment was a reduction of 25.55% (SD 9.87, p<0.0001). These results were [redacted]

[redacted] It should be noted that this outcome was assessed using the DUS.

In trial RM-493-015, in the pivotal cohort in the FAS population, only 42% of responders (those achieving ≥ 5% weight loss) lost ≥ 10% of their weight. To attain a better representation of the clinical efficacy of setmelanotide, the ERG considered that all patients that received the active study treatment should have been included in this analysis. As this trial contained a placebo-controlled withdrawal period, reversal of weight loss was also reported: the mean weight gain over the withdrawal in both the pivotal and supplemental cohorts was [redacted], and 4.974 kg in the pivotal cohort alone.

The mean baseline body weight at baseline for the DUS population was 131.7 kg, dropping to 115 kg at 52 weeks, representing a reduction of 12.5%.In the pivotal cohort, 5/11 (46%) met the 35% success criteria, while in the FAS, when both pivotal and supplementary patients are considered, 8/15 (90% CI 30.00, 75.63, p<0.0001) of the patients achieved a ≥10% weight loss across approximately one year of treatment.

In the extension trial RM-493-022 the weight loss of the patients was compared to the baseline weight of the index trial, where the [redacted] However, compared to the baseline mean weight at the start of the extension trial, the mean (SD) weight had increased from 91.56 (17.895) kg [redacted] The ERG noted the possible waning effect of setmelanotide, and the high levels of uncertainty of the ongoing clinical benefits.

Percentage body fat

In trial RM-493-011, the reduction in body fat mass from baseline to the end of the main study (12 or 13 weeks) was 23.2% for patient 1 and 17.9% for patient 2 in the POMC population[33]. Data for this outcome in the LEPR population were not reported in the publication by Clement et al[34].

In trial RM-493-012, there was a 38.64% mean reduction in body fat mass from baseline to 52 weeks (SD 15.30, p<0.0001) in the pivotal DUS cohort. The reduction was [redacted]

In trial RM-493-015, there was a mean reduction in body fat mass of [redacted]

At the beginning of the extension study, RM-493-022, the mean (SD) body fat was [redacted] but the percentage body fat is not reported, nor is body fat measurements throughout the study. The ERG noted that the CSR details that [redacted] but gave no figures to support this statement.

Waist circumference

In trial RM-493-011, the mean reduction in waist circumference was 11.50 (SD 6.36) cm for POMC patients and 6.67 (SD 4.04) cm for LEPR patients.

In trial RM-493-12, mean (SD) waist circumference at inclusion was 118.9 (17.6) cm and at around one year of treatment was 100.5 (12.4) cm, change -14.9% (7.6); 90% CI -18.4, -11.4, p<0.0001). This outcome was assessed in the DUS.

In trial RM-493-015, the reduction of waist circumference was statistically significant with a reduction of 7% (90% CI -9.93, -4.05: p=0.0002) from baseline, however, the change in waist circumference during the withdrawal period has not been reported, meaning that while a change in waist circumference from 127.3 (±22.46) cm at baseline to 114.4 (±20.03) cm at 52 weeks is a substantial decrease, there is no comparison for this change during the control period, adding to the uncertainty around the evidence base.

The results from the extension trial RM-493-022 show that while the lower waist circumference is maintained, the level of reduction falls, and almost stagnates entirely. At the start of the extension study, [redacted] This again suggests the possibility of a weight loss plateau with setmelanotide, and due to the short follow-up of 37 weeks in the extension study, there is large area of uncertainty of the long-term clinical efficacy of the study treatment.

Hunger

In trial RM-493-011, it is reported that hunger scores improved significantly for both patients in the POMC population[33], but exact numerical values were not reported. For the LEPR

population, as shown in Figure 1 of Clement et al[34], hunger scores improved on setmelanotide, and worsened during off-drug periods.

In trial RM-493-012, the mean percent change in the highest hunger score from baseline to approximately one year of treatment in patients aged at least 12 years in the DUS pivotal cohort was a reduction of 27.1% (SD 28.11, p=0.0005). The values were [redacted] A 25% reduction in hunger score over this time period was experienced by 4/8 (50%, 90% CI 19.29, 80.71, p=0.0004) responder patients aged at least 12 years in the pivotal cohort in the FAS. The values were [redacted]

In trial RM-493-015, daily worst hunger in 24 was measured in the pivotal cohort in the DUS population, where a least-squares mean % change from baseline in hunger score was -41.9% at approximately one year. The ERG acknowledged that the DUS population only includes responders to setmelanotide, and by using the DUS population for analysis of this endpoint the efficacy outcomes may be overstated.

Another key endpoint of trial RM-493-015 was the percentage of patients achieving at least 25% improvement in hunger scores, which was measured in the FAS population. Eight of the 11 (73%) pivotal cohort patients achieved this.

The company provided a singular hunger score in the extension study RM-493-022, with the mean hunger score of the 7 POMC patients at 8 at baseline of the index study, reducing to 6.43 at baseline of the extension study. [redacted] that both the weight loss and hunger score reduction plateaus with prolonged use of setmelanotide.

Incidence of type 2 diabetes

The incidence of type 2 diabetes was not reported in the included studies. However, glucose parameters, which are a marker of diabetes, were reported in RM-493-012, RM-493-015 and RM-493-022, but not RM-493-011.

In trial RM-493-012, fasting blood glucose fell from mean (SD) 135.8 (107.7) mg/dL at inclusion to 107.0 (85.5) mg/dL at around one year of treatment, change -17.2% (18.8), 90% CI -28.1, -6.3, p=0.018. Percentage HbA1c fell from mean (SD) 6.1% (1.8) at inclusion to 5.8% (1.9) at around one year of treatment, change -4.0% (10.5), 90% CI -10.1, 2.1, p=0.26; HbA1c, measured in mmol/mol, fell from mean (SD) 43.5 (20.5) mmol/mol at inclusion to 39.1 (23.6) mmol/mol at around one year of treatment, change scores and statistical significance not reported; and insulin during oral glucose loading fell from mean (SD) 136.0 (104.6) nmol/L at inclusion to 78.8 (104.1) nmol/L at around one year of treatment, change scores and statistical significance not reported.

In trial RM-493-015, fasting blood glucose increased from mean (SD) 106.1 (49.2) mg/dL at inclusion to 108.9 (55.4) mg/dL at around one year of treatment, change -0.7% (7.0), 90% CI -5.0, 3.7, p=0.78. Percentage HbA1c fell from mean (SD) 5.7% (0.8) at inclusion to 5.5% (0.7) at around one year of treatment, change -4.9% (7.8), 90% CI -12.3, 2.6, p=0.24); HbA1c, measured in mmol/mol fell from mean (SD) 54.8 (40.9) mmol/mol at inclusion to 53.8 (38.8) mmol/mol at around one year of treatment, change scores and statistical significance not reported; and insulin during oral glucose loading fell from mean (SD) 134.9 (104.3) nmol/L at inclusion to 129.5 (40.9) nmol/L at around one year of treatment, change scores and statistical significance not reported. The ERG noted that while fasting blood glucose is described as having increased, the change score has a negative sign. The ERG has checked and these values and their interpretation are the same in the CS and the Clement et al 2020 paper[35]. The ERG would like to flag this unresolved discrepancy in the company results.

The mean fasting glucose levels in trial RM-493-022 were only reported at patient level in mmol/mol, but the mean (SD) has been calculated and converted by the ERG in order to compare across trials. The mean (SD) fasting glucose fell from 75.367 (4.57) mg/dL at baseline to 74.88 (4.57) mg/dL at 37 weeks, showing only a 0.65% decrease. Percentage HbA1c was reported at the individual patient level. The mean (SD) calculated by the ERG was 4.85% (0.21) at baseline, increasing to 5.24% (0.19) at week 37, representing a 7.82% increase. Insulin oral glucose was not reported.

Cardiovascular events

No cardiovascular events results were reported in the included trials.

Mortality

No mortality results were reported in the included trials.

Health-related quality of life

In trial RM-493-011, as reported in the publication by Kuhnen et al 2016[33], it is stated that both patients experienced a 'dramatic' improvement in HRQoL, although numerical values are not provided to support this. QoL data for the LEPR population were not reported in Clement et al 2018[34]

In trial RM-493-012, for patients aged 18 and over [redacted] in the pivotal DUS cohort, there was a mean (SD) increase of [redacted] in the total IWQOL-Lite score with a score of [redacted] at 52 weeks vs. [redacted] at inclusion, i.e., a significant difference between the two scores [redacted] The company reported that this exceeded the minimal clinically important difference. For [redacted] paediatric patients aged 8 to 12, there was a significant mean improvement of [redacted] in total PedsQL score [redacted] assessed by children and [redacted] assessed by parents. For [redacted] paediatric patients aged 13 to 18, there was a significant mean improvement of [redacted] in total PedsQL score [redacted] assessed by children and a non-significant improvement of [redacted] assessed by parents.

In trial RM-493-015, mean increase in IWQOL-Lite score for patients aged 18 and over from baseline to 52 weeks was [redacted] Paediatric QoL data were not available at the data cut reported in the CS. This represents an area of uncertainty.

No HRQoL data for carers were reported in the included trials.

The ERG considered the lack of numerical data for this outcome an important omission from the clinical evidence base, and also noted that there are no data of the HRQoL for carers, as included in the NICE scope.

Co-morbidities

No co-morbidity outcome results were reported in the included trials. Trials reported certain co-morbidities only as a baseline measure.

Adverse effects

The company summarized data for adverse events in the CS (Document B, Section 9.7): Table 56 (RM-493-012), Table 58 (RM-493-015), Table 60 (RM-493-011) and Table 62 (RM-493-022). Below, the ERG presents data relating to AEs in depth due to discrepancies and inconsistencies in company reporting of AEs.

The ERG noticed certain discrepancies in the company's adverse event reporting, on which further explanation was sought from the company at the clarification stage. The company decision problem (CS, table 1) justified the company's decision to not include AEs in the company model by claiming that "no serious treatment related AEs were reported in the clinical trials and none of the AEs reported led to withdrawal or death. Any serious adverse events (SAEs) reported were not considered related to setmelanotide treatment" (CS, Table 1). However, the ERG noticed that, e.g. in RM 493-015 (CS, Table 57), "treatment-emergent adverse events" are shown - totaling [redacted] events, of which [redacted] were serious, one of which led to a patient being withdrawn due to Grade 1 eosinophilia that was deemed related to the study drug. In response to the ERG's clarification question A4, the company indicated that its initial statement on this matter was incorrect. The company further indicated that "it would be correct to say that across the four clinical trials, no SAEs were reported that were considered related to study drug." The ERG considered that this response did not satisfactorily address the issue of "treatment-emergent adverse events".

The ERG also noted that the company provided AE data using safety analysis sets for all included trials, including all participants who received at least one dose of study medication. The ERG acknowledges the challenge in determining safety in small sample sizes but considered this approach to represent the least conservative picture as AEs are reported as proportions of the largest population possible. In addition, for RM-493-011, this population included two participants with epigenetic (POMC hypermethylation) obesity not eligible within the NICE scope, as evidenced by their exclusion from the clinical effectiveness results. Therefore, the ERG considered conclusions around AEs associated with a lifetime of treatment with setmelanotide to be very uncertain and deemed details of AEs to be of particular importance.

All patients in all four trials experienced at least one adverse event relating to setmelanotide. In trial RM-493-015, most were mild or moderate in nature, but [redacted] patients experienced a serious treatment-emergent adverse event (TEAE) and [redacted]

Table 32 in the CSR for trial RM-493-015 shows that all patients in both the pivotal and supplemental cohort experienced at least [redacted] most common were 'general disorders and administration site conditions', where [redacted] of patients in both cohorts experienced at least [redacted] treatment related TEAE. These included most commonly injection site erythema, pruritus, induration, pain, oedema and bruising. [redacted] in RM-493-015, [redacted] of patients in trial RM-493-011 and [redacted] patients [redacted] in trial RM-493-012 experienced a treatment related TEAE relating to skin and subcutaneous tissue disorders, including skin hyperpigmentation [redacted] which has been identified by clinicians as a possible future reason for withdrawal, as darkening of the skin tone can be undesirable for patients.

Serious TEAEs for Trial RM-493-015 are detailed in Table 33 in the CSR, but the company have not specified if these were deemed as related to the study drug. [redacted] another patient experienced grade 1 gastric band reversal and suicidal ideation on day 292, which had progressed from a mild depression. One patient sustained fatal road traffic injuries.

[redacted] Due to the small patient numbers in this trial, the rates of eosinophilia in patients on setmelanotide cannot be determined and may have implications on the real-world use rates.

Findings from trial RM-493-011 were considered to be consistent with the rates of AEs reported in RM-493-015. The most common TEAE was gastrointestinal disorders [redacted], general disorders and administration site conditions [redacted] and hyperpigmentation [redacted]. However, due to the small sample size, the company did not provide and analysis of adverse events in this trial. The ERG recognized that the small sample sizes increased the challenges of analysis, but with 7 patients, simple analysis may have been possible. The TEAEs that were reported by at least three POMC/PCSK1 and LEPR patients were: dry mouth, injection site reactions, hyperpigmentation and headache.

Trial RM-493-012 was also similar; [redacted] patients treated with setmelanotide experienced at least one TEAE; [redacted] patients reported with an SAE during the study, [redacted] deemed related to

setmelanotide. Like the other trials, the company did not provide detail on how this determination is made. The most common TEAEs reported were skin hyperpigmentation [redacted], injection site erythema [redacted], injection site oedema and pruitius [redacted], and headache, nausea and vomiting[redacted].

In trial RM-493-011, serious adverse events were presented in Table 18 in the CSR [redacted] With such small patient numbers in all four trials, there is a large amount of uncertainty around the treatment related adverse events.

In the extension trial RM-493-022, all TEAEs were considered mild, and none required adjustment of dosing. [redacted] The unpublished data for this study (Table 61 of the CS) indicated that [redacted] patients experienced at least one TEAE, [redacted] each [redacted] reported an SAE and withdrew from the study. Though not deemed related to the study drug by the company, [redacted] patients reported on in the CSR also experienced an upper respiratory tract infection; unpublished data for this study, reported in Table 62 of the CS, indicated that [redacted] patients reported upper respiratory tract infections.

Despite the majority of patients in all earlier trials reporting injection site reactions, this was not recorded as a TEAE in the extension study. On further investigation into injection site reactions, all seven patients with POMC deficiency included in this trial reported mild injection-site reactions (ISRs) during the extension trial. Similarly, [redacted] but this was also not recorded as TEAEs during the extension study. The ERG note the lack of reporting of ISRs and hyperpigmentation as TEAEs and because of this, the TEAEs reported are not fully represented in the extension trial.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison and/or multiple treatment comparison was undertaken by the company for this appraisal. The ERG's critique of this decision is provided below in Section 3.4.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparisons or multiple treatment comparisons were undertaken by the company for this appraisal. The rationale provided was that there was no direct comparative evidence for setmelanotide against the comparator in the company scope (see Section 2.3 for discussion of the company's narrowing of the NICE scope in terms of comparators) and the absence of evidence for the treatment effect of the relevant comparator – standard management without setmelanotide (conceptualised based on clinical advice as diet and exercise based interventions). Clinical advisors to the ERG were not aware of any published evidence assessing the clinical effectiveness of standard management in the context of LEPR or POMC associated obesity. Clinical advice was nevertheless that standard management – as currently used in routine practice – is not considered effective for this indication, because it does not address the biological underpinnings of LEPR- or POMC-associated obesity. Furthermore, setmelanotide is co-administered with standard management in the company trials, which complicates the generation of efficacy estimates comparing setmelanotide with standard management. While the ERG considered the company's decision not to conduct an indirect or multiple treatment comparison to be appropriate, given the absence of relevant data to inform such a comparison, the ERG nevertheless considered it a substantial limitation that no direct or indirect evidence was available to compare setmelanotide and standard management in the appraisal population. The ERG's comment on clinical inputs to the model can be found in Section 4.2.6.

3.5. Additional work on clinical effectiveness undertaken by the ERG

The company did not search a range of clinical trials sources and search terms were not reported. The ERG therefore carried out some additional searches for clinical trials in the WHO trials register, the EU trials register and in Scan Medicine (NIHR). Search terms were for genetic obesity, LEPR and POMC; 39 possible trials were identified. Screening of this yield resulted in the identification of 11 potentially eligible trials: two of these were not yet recruiting participants (NCT04963231 and NCT04966741); eight were trial registries associated with trials included in the CS (duplicate entries were found for clinicaltrials.gov and the EU trials register); and two were duplicate records linked to an ongoing study (NCT03013543 and 2017-000387-14/ES for clinicaltrials.gov and EU trials register, respectively) identified in Section 4.1 (p.13 of the CS). The ERG concluded that the company included all relevant clinical effectiveness evidence in their submission.

The company's searches were not thorough enough to be certain that all adverse events had been identified. The ERG therefore carried out additional searches in Medline and Embase, using terms for setmelanotide (as the original searches did not include this term); 100 papers were identified. Screening of this yield resulted in the identification of nine eligible publications: two of these were duplicate records of publications already included (Kühnen et al 2016[33] and Clément et al 2020[35]); five were additional publications reporting on or referencing the results of RM-493-011; one was an abstract reporting on the findings of RM-493-022; and another was an abstract reporting on the results published in Clément et al 2020[35]. These records either predated the sources included in the CS or cited these; no inconsistencies were found in the reporting between these records and the CS, with the exception of updated numbers in the latter. The ERG concluded that the company included all relevant safety evidence of treatment with setmelanotide in the population of interest.

3.6. Conclusions of the clinical effectiveness section

The ERG considered the company's SLR to be generally acceptable. Searches were not considered to be thorough, meaning the ERG could not exclude the possibility that relevant evidence had been excluded. However, the ERG did not itself identify any additional relevant studies.

The ERG considered that the company decision problem generally corresponded adequately to the NICE scope. However, the ERG noted that the company considerably narrowed the outcomes in its decision problem compared to the NICE scope, which impacted upon the clinical effectiveness evidence to be considered in the appraisal.

In addition to the key issue relating to the narrowing of outcomes in the decision problem, the ERG noted three key issues with the clinical effectiveness evidence:

- Company trials did not report all outcomes in company decision problem
- No direct or indirect evidence presented comparing setmelanotide with standard management in a population of obesity associated with POMC and/or LEPR deficiency
- Dosing in the included trials is not consistently in accordance with the intended UK dosing

The fact that no patients in the extension trial RM-493-022 received setmelanotide at the anticipated UK dose of 3.0 mg, while German patients in the index trials were capped at 2.5 mg by regulatory authorities, contributes to concerns over the generalisability of the evidence to a

UK decision making context. However, ethnicity and differences in treatment pathways beyond dosing are not expected to play an important role in this appraisal, according to clinical advice to the ERG.

The ERG agreed that overall the trial evidence as presented in the CS, CSRs and trial publications does support a benefit for setmelanotide on key outcomes in this appraisal within the follow-up periods as assessed. However, it is important to consider this in the context that data were not available from all scoped outcomes and that the trial follow-up periods were short. Moreover, evidence from the extension trial RM-493-022 showed that the benefit associated with setmelanotide in terms of BMI and weight loss plateaued within the two-year follow-up period, adding to the uncertainty regarding the long-term benefits of setmelanotide, in the context of the company's expectation of life-long use. As described in Section 2.2, the ERG also noted that the introduction to the CS outlined a steeper up-titration protocol than featured in the index trials. This adds to uncertainty regarding the generalisability of the trial evidence.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the section also contains summaries and critiques of other reviews related to cost effectiveness presented in the company submission. Therefore, the following section includes description and critique of searches for a) the cost effectiveness analysis review, b) measurement and evaluation of health effects and c) cost and healthcare resource identification, measurement and valuation.

The company undertook a SLR to identify evidence for outcomes relevant to the cost-effectiveness, as summarised in Table 12: prior cost-effectiveness analyses, measurement and evaluation of health effects and cost and healthcare resource identification, measurement and valuation of setmelanotide for treating obesity caused by LEPR or POMC deficiency. The inclusion criteria were appropriately relevant to the decision problem, and the methods used to conduct the reviews were of an appropriate standard. A few minor issues were identified; however, scrutiny of the company's SLR report and the CS indicated no cause for concern.

Table 12. Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence and evidence reporting cost and healthcare resource identification, measurement and valuation

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix 3, Section 1.3.1 to Section 1.3.5 and Appendix 1	The searches are the same as for clinical effectiveness and the assessment is the same (Table 7). Hand searching was conducted for previously developed cost-effectiveness models used in obesity-related NICE submissions.
Inclusion criteria	Appendix 3, Table 7	The inclusion criteria for the cost-effectiveness review were considered appropriate to the decision problem.
Screening	Not reported	No information provided
Data extraction	Appendix 3, Section 1.3.7	Data extraction was conducted to appropriate standards to minimise selection bias, with single reviewer extractions checked by a second reviewer and arbitration conducted by a third, if necessary.
Evidence summary	CS, Section 11.1.3	No studies evaluating the economic burden of disease or the cost-effectiveness of interventions for the treatment of obesity caused by POMC/PCSK1 or LEPR mutations was identified during the SLR. The ERG considered that the company were unlikely to have

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		missed any important studies and considered the company's conclusions as appropriate.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; LEPR, leptin receptor; NICE, National Institute for Health and Care Excellence; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SLR, systematic literature review

The company reported a hand search of previously developed cost-effectiveness models used in obesity-related NICE submissions which identified four prior technology appraisals (Table 13).

Table 13. Summary of NICE technology appraisals in obesity-related indications

Technology appraisal	Year	Indication	Model structure
HST14[39]	2021	Metreleptin for treating lipodystrophy	Individual patient-level simulation and partitioned survival model for mortality
TA664[40]	2020	Liraglutide for managing overweight and obesity	Markov cohort state transition model
TA494[41]	2017	Naltrexone–bupropion for managing overweight and obesity	DES
TA144[42] (guidance withdrawn, licence for rimonabant withdrawn)	2008	Rimonabant for the treatment of overweight and obese adults	Markov cohort state transition model and DES

Abbreviations: DES, discrete event simulation; HST, highly specialised technology; TA, technology appraisal

A summary of the ERG's critique of the methods used by the company to identify evidence on the measurement and evaluation of health effects is presented in Table 14.

Table 14. Summary of ERG's critique of the methods implemented by the company to identify evidence reporting the measurement and evaluation of health effects

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix 5, Section 1.5.1 to Section 1.5.5 and Appendix 1	The searches are the same as for clinical effectiveness and the assessment is the same (Table 7). Hand searching was conducted for previously developed cost-effectiveness models used in obesity-related NICE submissions.
Inclusion criteria	Appendix 5, Table 9	The inclusion criteria were considered appropriate to the decision problem.
Screening	Not reported	No information provided

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data extraction	Appendix 5, Section 1.5.7	Data extraction was conducted to appropriate standards to minimise selection bias, with single reviewer extractions checked by a second reviewer and arbitration conducted by a third, if necessary.
Evidence summary	CS, Section 10.1.5 and Section 10.1.6	Three studies were eligible for inclusion. The ERG considered that the company were unlikely to have missed any important studies and considered the company's conclusions as appropriate. Given that no studies were identified that reported utility values for the population of interest, utility values were sourced for the general obesity population and the company provided details for an additional four studies. The company did not provide information as to whether these studies were identified using systematic review methodology. The ERG is unable to comment whether the identified studies represent all relevant literature.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

The NICE reference case checklist for the submission, along with the ERG's comment for each checklist attribute, is summarised in Table 15.

Table 15: NICE reference case checklist

Attribute	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were estimated for patients. The model did not include carer disutility. See Section 4.2.6.5 and 6.2.7 for further comment.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon (100 years) was used in the base case analysis. The ERG considered a lifetime horizon to be reasonable. However shorter time horizons were explored to determine the impact on the results.

Attribute	Reference case	ERG comment on CS
Synthesis of evidence on health effects	Based on systematic review	The clinical data used to estimate the effectiveness of setmelanotide in the economic model were based on data from the single arm phase 3 studies RM-493-012 and RM-493-015. Due to the lack of long term clinical data the company made several assumptions surrounding long term treatment effectiveness See Section 4.2.6.1.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	SF-36 data were collected in the phase 3 studies; however the company did not use these data in the economic model. For adult patients, baseline health state utility values were derived from a published study by Alsumali et al[43], which collected data using the SF-12 and mapped values to EQ-5D. For paediatric patients with a BMI Z-score 0.0-0.1 and 3.5-4.0, the company estimated utilities based on the Paeds-QL score, reported in a published study by Riazi et al[44]. These utilities were then mapped to EQ-5D values using a published algorithm by Khan et al[45]. For the remaining health states (BMI Z-score 1.0 to 3.5), values were linearly extrapolated. Utility multipliers associated with mild, moderate and severe hyperphagia were estimated based on vignettes which elicited responses from members of the UK public. As such values were not derived from patients with POMC/PCSK1 and LEPR. The ERG considered the lack of direct HRQoL data (particularly with respect to hyperphagia) in patients with POMC/PCSK1 and LEPR to be a limitation.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The ERG had concerns surrounding the source of preference data for valuing changes in HRQoL. See Section 4.2.6.5.

Attribute	Reference case	ERG comment on CS
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns in the company's base case i.e. QALY weighting was not implemented.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were mostly valued using PSSRU, which was considered appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs were discounted at 3.5% and benefits were discounted at 1.5%. Due to the lack of mortality data from the relevant clinical trials, the ERG noted that there is considerable uncertainty surrounding the modelled life year gain associated with setmelanotide. ERG preference was therefore to use NICE reference case discounting for benefits at 3.5%.

Abbreviations: BMI, body mass index; CS, company submission; eMIT, electronic Market Information Tool; EQ-5D, EuroQol 5 dimension; ERG, evidence review group; HRQoL: health-related quality of life; HST, highly specialised technology; LEPR, leptin receptor; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PCSK1, proprotein convertase subtilisin/kexin type 1; Peds-QL, Paediatric Quality of Life Inventory; POMC, proopiomelanocortin; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Health Survey; TA, technology appraisal

4.2.2. Model structure

The company submittted a de novo Markov model, consisting of health states which were defined according to BMI (for adults) and BMI Z-score for children. These health states were defined as BMI ranges with a five-point spread (e.g., 30-35, 35-40, etc.) or BMI Z-score ranges with a 0.5 point spread (e.g. 3.0-3.5, 3.5-4.0 etc.). The company stated that these aligned generally with NICE guidelines. Death was included as an absorbing state.

Patients entered the model as responders i.e. all pateints received setmelanotide. From 12 weeks, patients were considered to repsond or not respond to treatment based on response rates from RM-493-012 and RM-493-015. The company estimated the overall response rate for POMC/PCSK1 adult and paediatric patients to be 86% and for LEPR adult and paediatric patients, this was 60%.

Responders were treated with setmelanotide and BSC, whilst non-responders received BSC alone. Each health state was associated with the resource use costs for the treatment of obesity and the relevant obesity related complications and the relevant health state utilities (based on

BMI class), utility multiplier for hyperphagia and the disutilities associated with the co-morbidities. The company assumed that LEPR and POMC/PCSK1 patients experienced BMI gain as paediatric patients, but that their BMI did not change substantially after reaching adulthood. Once paediatric patients reached 18 years (adulthood), the company mapped the BMI Z-scores to corresponding adult BMI class, based on a published mapping equation by the World Health Organisation (WHO), based on UK statistics.

The ERG noted the following uncertainties surrouding the company's modelling approach:

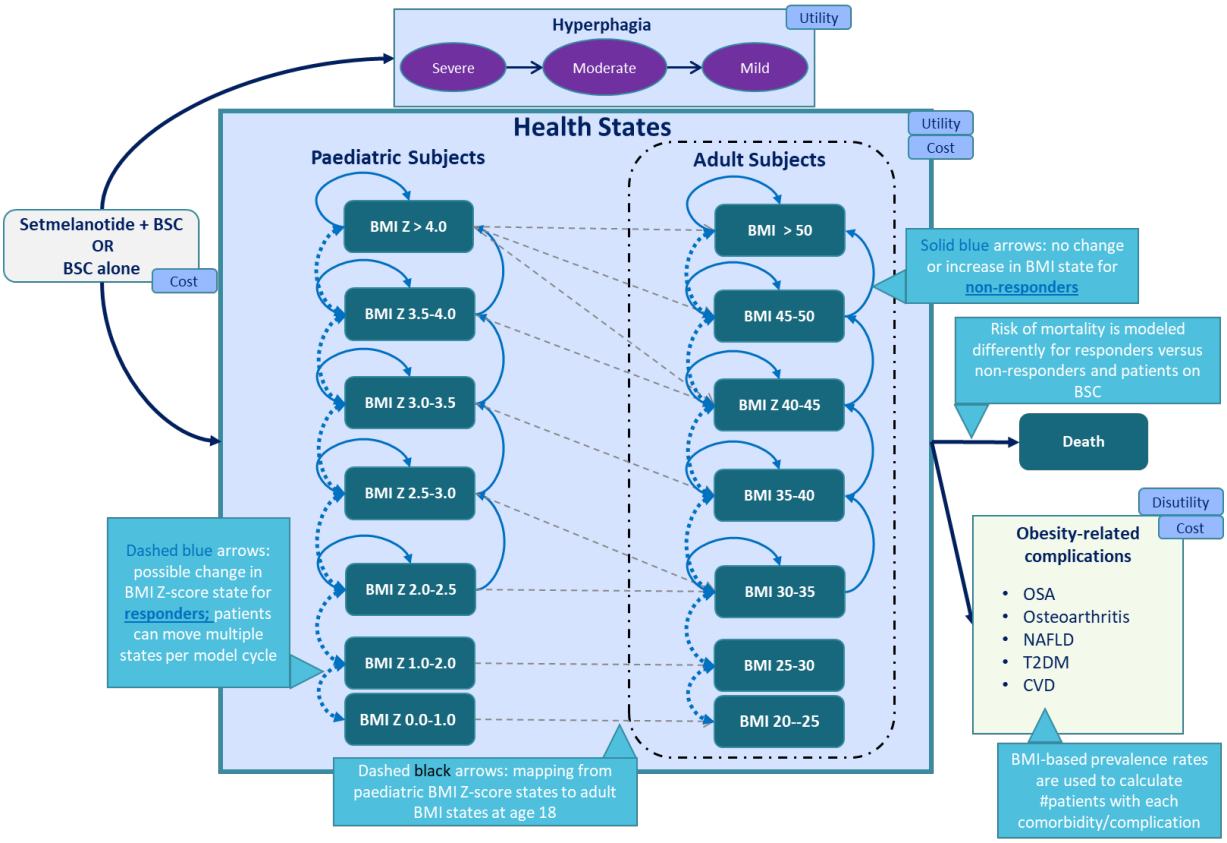
- During the clarification stage, the ERG queried the company's rationale for deviating from the model structure reported in Ara et al. 2012[46], a systematic review of clinical and cost effectiveness of using drugs in treating obese patients in primary care, which informed the model structure in some of the previous obesity related appraisals (NICE technology appraisal (TA) TA494[41] and TA664[40]). The company responded stating that Ara et al. 2012[46] included excessive granularity in the representation of type 2 diabetes mellitus (T2DM) and cardiovascular disease and insufficient detail surrounding other key complications arising from defects in the MCR4 axis, including obstructive sleep apnoea, osteoarthritis, non-alcoholic fatty liver disease and especially in the case of LEPR-deficient subjects, early mortality compared to subjects with general obesity. Given the model structure used is based on BMI class-based health states (see Figure 1), the ERG considered it to be suitable for the decision problem concerned, although there are simplifying assumptions especially related to hyperphagia which introduce uncertainty.

- The model does not account for any correlation between BMI class and hyperphagia status i.e. a patient's hyperphagia status is not assumed to be impacted by a change in BMI. Within the model, hyperphagia status (mild, moderate and severe), is considered as a condition within each BMI/BMI Z-score health state. The company stated that in order to include these interactions, more patient level data would be required and additional complexity would need to included. Overall, the ERG considered the company's approach to be simplistic and the impact of correlation between BMI class and hyperphagia status on the chosen structure remains unexplored.

- Modelled BMI class health states and the baseline distribution of patients across these health states appeared to be informed by the pivotal studies RM-493-012 and RM-493-015. The ERG noted that the model does not include granular BMI class health states above 50 BMI for adults and 4.0 for paediatric patients i.e. for adults this is modelled as >50 BMI and

for paediatrics this is modelled as >40 BMI Z. The company justified this on the basis that there were limited published data with respect these severely obese patients and therefore assumptions and/or data from general obesity patients would have to have been used, thus adding to uncertainty. The ERG acknowledged the company's justification, however based on clinical input to the ERG, in practice a proportion of patients may fall into higher (more granular) BMI classes. The model therefore does not appear to capture all relevant health states.

Figure 1: Model structure



Abbreviations: BMI, body mass index; BSC, best supportive care; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; OSA, obstructive sleep apnoea; T2DM, type 2 diabetes mellitus

4.2.3. Population

4.2.3.1. Modelled patient characteristics

Modelled BMI baseline distribution for both adults and paediatric patients with POMC/PCSK1 and LEPR were taken from the RM-493-012 and RM-493-015 trials (Table 17 and Table 18), whilst the baseline distribution of POMC/PCSK1 and LEPR (and proportion of adult and

paediatric patients) were derived from published studies (see Table 16). The baseline distribution of adult and paediatric patients was based on data from a conference abstract by Argente et al 2019[47], whilst the baseline distribution of POMC/PCSK1 and LEPR patients was based on a study by Graves et al[48]. As the full study by Argente et al[47] was not available, the ERG was unable to review the source and comment on its appropriateness. The ERG was unclear why the company opted to use a conference abstract to inform the economic model (as opposed to direct trial data from RM-493-012 and RM-493-015). Based on a review of the Argente et al[47] abstract, it appeared to include a higher number of patients, and therefore may have been considered more robust by the company.

To explore uncertainty surrounding modelled patient characteristics, the company conducted one-way sensitivity analyses for the overall population which altered the distribution of paediatric patients by +/- 10% and the % of patients with POMC by +/- 10%. This had minimal impact on the ICER. Furthermore, the company conducted scenario analyses whereby baseline distribution of POMC and LEPR, as well as the baseline distribution of adult and paediatric patients were based on the trial population. The ERG noted that results were not especially sensitive to these analyses; however, the company did not provide these results for the individual subgroups, which introduced uncertainty.

Table 16: Modelled baseline characteristics (overall population)

	POMC/PCSK1 deficiency	LEPR deficiency
Distribution	33.3%	66.7%
	Distribution	
Adult	26%	
Paediatric	74%	

Abbreviations: LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Table 17: Modelled BMI baseline distribution (paediatric patients)

BMI Z-score	POMC/PCSK1 deficiency	LEPR deficiency
0.0-0.1	[redacted]	[redacted]
0.1-2.0	[redacted]	[redacted]
2.0-2.5	[redacted]	[redacted]
2.5-3.0	[redacted]	[redacted]
3.0-3.5	[redacted]	[redacted]

BMI Z-score	POMC/PCSK1 deficiency	LEPR deficiency
3.5-4.0	[redacted]	[redacted]
>4.0	[redacted]	[redacted]

Abbreviations: BMI, body mass index; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Table 18: Modelled BMI baseline distribution (adult patients)

BMI Z-score	POMC/PCSK1 deficiency	LEPR deficiency
20-25	[redacted]	[redacted]
25-30	[redacted]	[redacted]
30-35	[redacted]	[redacted]
35-40	[redacted]	[redacted]
40-45	[redacted]	[redacted]
45-50	[redacted]	[redacted]
>50	[redacted]	[redacted]

Abbreviations: BMI, body mass index; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

In the base case analysis, the company presented economic results for an overall population i.e. a single ICER was provided representing the cost effectiveness of setmelanotide plus BSC compared to BSC alone, in POMC/PCSK1 and LEPR. The ERG sought clinical input surrounding the appropriateness of presenting results for an overall POMC and LEPR population. Based on clinician input to the ERG, an overall population was not considered to be appropriate, given that there are differences in treatment effect and natural disease progression between POMC/PCSK1 and LEPR patients (and differences in disease progression and related co-morbidities between adult and paediatric patients). Furthermore, the overall results do not represent a clinically coherent patient group. The company submitted subgroup analyses which further disaggregated results according to disease type and age (see Table, p.217 of the CS). The ERG considered these results to be more appropriate.

4.2.4. Interventions and comparators

The comparator used in the economic evaluation was best supportive care (BSC), which included diet advice and lifestyle management. The company stated that in the UK, BSC for patients with genetic mutations defaults to general obesity care, which includes the use of lifestyle and dietary interventions as well as behavioral therapy (as per the NICE guideline

CG189[12]). In the CS the company stated that other comparators such as orlistat, methylcellulose, and bariatric surgery are not routinely used in clinical practice in individuals with obesity associated with LEPR and POMC/PCSK1 deficiencies, and therefore were not included as comparators within this appraisal.

Based on clinical input to the ERG, BSC was broadly considered to be the most appropriate comparator and the most relevant for inclusion within the economic analysis. However, bariatric surgery was identified as a potentially relevant comparator by one clinician. The ERG considered that bariatric surgery could not be accommodated as a relevant comparator in the economic model in a meaningful way; the company would likely have to revise the model structure given the fundamental differences between economic modelling of surgical and medical interventions. Overall, the ERG were satisfied with the selection of BSC as the base case comparator.

4.2.5. Perspective, time horizon and discounting

The time horizon used in the base case was 100 years or a lifetime horizon. The company justified the use of a lifetime horizon on the basis that it reflects NICE HST guidance i.e. that it reflects the chronic nature of POMC/PCSK1 and LEPR-deficiency, allowing full costs and benefits to be captured over the survival time of all patients. The ERG considered the company's rationale to be reasonable and acknowledged that a lifetime horizon is likely to be appropriate. The company presented sensitivity analysis which reduced the time horizon to 10 and 20 years. Results were highly sensitive to these values, indicating that large proportion of the modelled incremental QALY gain associated with setmelanotide is accrued over the latter stages of the modelled time horizon.

The ERG noted that costs were discounted at 3.5% as appropriate, however benefits were discounted at 1.5%. Based on the NICE HST interim methods process guide (2017)[49], discounting benefits at 1.5% may be considered reasonable if the treatment restores patients to near full or near health when they would otherwise die or have a severely impaired life. The ERG opined that the use of non-reference case discounting may be appropriate if there is robust evidence to support modelled treatment effectiveness estimates. However, due to the lack of robust data with respect to the long-term effectiveness of setmelanotide and impact on mortality (i.e. mortality gains are strictly modelled rather than evidenced in the included trials), there is considerable uncertainty surrounding the modelled incremental life year and QALY gain. The company conducted a scenario analysis which applied a 3.5% discount to benefits and this

increased the ICER considerably. The ERG considered a discount rate of 3.5% to be more appropriate for decision making.

It is worth noting that the company has not applied QALY weighting within this submission. As stipulated in the NICE HST interim methods process guide (2017)[49], QALY weighting may be considered by the committee if there is compelling evidence that the treatment offers significant QALY gains. The ERG considered the long-term clinical effectiveness (and by extension the incremental QALY gain) associated with setmelanotide to be highly uncertain due to a lack of robust clinical data, therefore the omission of QALY weighting within the company's base appeared to be appropriate.

All costs and outcomes were estimated from an NHS and PSS perspective.

4.2.6. Evidence used to inform the company's model

4.2.6.1. Treatment effectiveness and extrapolation

The ERG identified uncertainty surrounding the treatment effect used in the model during trial period, the extrapolation of setmelanotide treatment effectiveness beyond the clinical trial duration for both POMC/PCSK1 and LEPR patients, and modelled parameters with respect to hyperphagia.

The company state that the setmelanotide treatment effect on natural weight gain trajectories was based on 52-week trial data (see Table 19). The ERG noted that data from the long-term trial RM-493-022 were not used to model treatment effectiveness and the company did not provide justification for excluding this study. Based on the studies as outlined in Clément et al 2020[35] 2020, the mean change in BMI for POMC/PCSK1 patients was a reduction of 27.8% (based on the designated use set and irrespective of age). For LEPR patients, patients experienced a mean change in BMI reduction of 13.0% (based on the designated use set and irrespective of age). Given that mean BMI at baseline for adults was estimated to be 40.4 (BMI class 40-45) for POMC/PCSK1 patients and 48.2 (BMI class 45-50) for LEPR patients, a 27.8% reduction corresponds to [redacted]) and [redacted]) respectively. Based on these results, the company's modelled treatment effectiveness estimates may be reasonable, however the ERG noted several concerns with these data i.e. small patient numbers and short trial duration, which suggest that results should be interpreted with caution.

In order to explore uncertainty surrounding the setmelanotide treatment effect on BMI during the clinical trial period, the ERG conducted a scenario analysis whereby BMI is assumed to drop by [redacted] for patients with POMC and [redacted] for patients with LEPR. See Section 6.2.9 for results.

Table 19: Modelled efficacy within the trial period

	Drop in BMI/BMI Z- score (POMC/PCSK1)	Drop in BMI/BMI Z- score (LEPR deficiency)
Paediatric	[redacted]	[redacted]
Adult	[redacted]	[redacted]
Based on published study	(NCT02896192/RM-493-012)	(NCT03287960/RM-493-015)

Abbreviations: BMI, body mass index; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Extrapolated setmelanotide treatment effect

As noted in Table 20, the company assumed that adult and paediatric patients with POMC/PCSK1 [redacted]. For LEPR patients, the company assumed that the treatment effect would be [redacted]. The ERG noted that these assumptions were not supported by long term clinical effectiveness data and that the company justified these assumptions based on clinical opinion. To validate these modelled treatment effectiveness estimates, clinical opinion to the ERG was sought. Based on clinical input received, clinical experts were broadly satisfied with the company's assumptions. However, the ERG considered that robust long-term clinical data are required to validate the company's modelled effectiveness estimates. The model allowed for the selection of alternative efficacy assumptions including BMI regain, although scenario analyses and probabilistic sensitivity analyses results testing alternative clinical effectiveness assumptions were not provided. In order to explore uncertainty surrounding the long-term extrapolation of setmelanotide treatment effect on BMI, the ERG has conducted scenario analyses which assumes BMI regain for both POMC/PCSK1 and LEPR patients and which assumes BMI maintenance after the trial period for patients with POMC/PCSK1. See Section 6.2.9 for results.

Table 20: Extrapolation of setmelanotide treatment effect

	Long term efficacy	Company rationale
POMC/PCSK1	[redacted]	Assumption based on clinical opinion

	Long term efficacy	Company rationale
LEPR deficiency	BMI maintenance (after trial duration)	Assumption based on clinical opinion

Abbreviations: BMI, body mass index; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

[redacted]

Modelled setmelanotide response rates

The percentage of patients who responded to treatment at 12 weeks from RM-493-012 and RM-493-015 was used to inform modelled response rates (see Table 21). Modelled post trial setmelanotide response rates were based on an overall population response rate approach i.e. for POMC/PCSK1 and LEPR, the company averaged the response rates across BMI class and BMI Z-scores to obtain an average response rate for adult and paediatric patients. The ERG did not consider this approach to be appropriate as the use of BMI class response better aligned with the company's model structure and provided a more granular assessment of response. During clarification (B7), the company was asked to comment on the rationale for using the overall response rate in the base case. Based on their response the company stated that using post trial efficacy defined by overall population response was considered to be more appropriate due to the lack of data and small patient numbers associated with estimating BMI class response. Overall, the ERG agreed with the company's justification. Furthermore the company's model allowed the user to conduct a scenario analysis whereby response rates could be estimated using BMI class. The ERG noted that results were not sensitive to this.

Table 21: Setmelanotide response rates during trial (overall response)

	POMC/PCSK1	LEPR deficiency
Paediatric	86%	60%
Adult	86%	60%

Abbreviations: LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Modelled impact on hyperphagia

Categorisation of hyperphagia

Treatment effectiveness with respect to the impact of setmelanotide on hyperphagia was not assessed directly in the clinical studies. The average hunger score one-year post treatment

recorded in the trials was used as a surrogate to determine the hyperphagia severity. These scores were based on a scale of 1 to 10 (inclusive), and this scale was used to derive cutoffs for different hyperphagia severities that were considered. The ERG noted some inconsistency surrounding the reporting of these cutoffs in the CS. On p.187 of the CS the company stated that a score of 0 to 2.99 (inclusive) translated to mild hyperphagia, 3 to 6.99 translated to moderate hyperphagia, and 7 to 10 translated to severe hyperphagia. However, on p.170 these cut offs differed i.e. a score of ≤ 4 translated to mild hyperphagia, 4 to 6 translated to moderate hyperphagia, and ≥ 7 translated to severe hyperphagia. Furthermore, the company derived the hunger score cut-offs and scale mappings from discussion with clinical experts who were consulted in the design of the vignette study; however, it was not clear to the ERG whether the descriptions of mild, moderate and severe used to derive the cut-offs were the same as those set out in the vignette study.

It is worth noting that in metreleptin for the treatment of lipodystrophy (HST 14)[39], hyperphagia was not categorised according to severity (but rather considered based on absence or presence). The company stated that the approach used in metreleptin was criticised by NICE and the ERG as it potentially underestimated the impact of hyperphagia on a patient's HRQoL. As such the company has taken a novel approach within this appraisal by stratifying according to severity. Clinical opinion to the ERG broadly agreed that a more granular assessment of hyperphagia may be reasonable; however there is uncertainty as to whether categorisation as per the company's definition within their vignettes is appropriate.

Modelled baseline distribution of hyperphagia

The baseline hyperphagia severity distribution in patients (mild, moderate or severe) in the company model was based on an assumption derived from the opinion of a UK clinical expert (Table 22). While clinical advice to the ERG suggested that the estimates used by the company were appropriate, it was not clear to the ERG whether the estimated distribution had been based on the descriptions of mild, moderate and severe hyperphagia from the vignette study outlined in Section 4.2.6.5. As such the extent to which the health states and respective distribution in the model were aligned with the descriptions of mild, moderate and severe disease (and associated utility multipliers) in the vignettes was not clear. The company did not conduct sensitivity analysis using alternative baseline distributions which is a source of uncertainty. The ERG asked its clinical experts to provide estimated proportions/distributions based on the health state definitions from the company's vignettes, these are outlined in (Table

22). To explore uncertainty surrounding modelled baseline hyperphagia distribution, the ERG conducted a scenario analysis (considered as a part of the combined hyperphagia scenario analysis explained in Section 6.2.5) which used the ERG clinician elicited values. See Section 6.2.9 for results.

Table 22. Baseline distribution across hyperphagia states

	Company		Clinical opinion to the ERG	
	POMC/PCSK1	LEPR	POMC/PCSK1	LEPR
Mild	[redacted]	[redacted]	10%	0%
Moderate	[redacted]	[redacted]	40%	0%
Severe	[redacted]	[redacted]	50%	100%

Abbreviations: ERG, Evidence Review Group; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Treatment effect on hyperphagia (hyperphagia transition probabilities)

As noted in Section 4.2.2, the model does not account for any correlation between BMI class and hyperphagia status, i.e. a patient's hyperphagia status is not assumed to be impacted by a change in BMI. Within the model, hyperphagia is not modelled as separate set of health states but treated as a condition within each BMI/BMI Z-score health state and assigned a separate utility corresponding to severity (mild, moderate, or severe).

The calculation of hyperphagia severity transition probabilities as outlined in Table 23 was based on an internal analysis by the company and details were not provided in the CS. During clarification, the ERG asked the company to further clarify how hyperphagia state transitions were derived (clarification question C1); however, the explanation was not considered satisfactory as precise calculations were not submitted to the ERG. Due to these uncertainties, the ERG conducted a scenario analysis (considered as a part of the combined hyperphagia scenario analysis explained in Section 6.2.5) which reduced the impact of setmelanotide on hyperphagia and presented results according to subgroups. See Section 6.2.1 for results.

Table 23: Treatment effect on hyperphagia (transition probabilities)

	POMC/PCSK1	LEPR
Severe to mild	[redacted]	[redacted]
Severe to moderate	[redacted]	[redacted]
Moderate to mild	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

The ERG noted that the treatment effect of setmelanotide on hyperphagia during the clinical trials was applied at the beginning of the first cycle for responders and persisted throughout the patients' lifetime (i.e. the treatment effect of setmelanotide was maintained after one year). Despite a lack of supporting clinical evidence in this respect, clinical advice to the ERG indicated that this was a reasonable assumption.

Finally, in the base case analysis, hyperphagia treatment effect was applied at the beginning of the first modelled cycle. The ERG did not consider the company's approach to this to be appropriate given that treatment effect/response was only measured after 12 weeks in the clinical trials. During clarification, the company stated that this was a simplifying assumption and subsequently updated their model to allow the user to delay the impact on hyperphagia till the end of the first cycle. The ERG considered this to be more appropriate and accepted this as a correction in the model.

4.2.6.2. Treatment duration and discontinuation

Treatment discontinuation was not explicitly modelled by the company and rationale was not provided for this omission. Based on RM-493-015, one of the 15 patients discontinued treatment with setmelanotide, whilst three patients in study RM-493-012 discontinued. During clarification, the company stated that the patient from RM-493-015 discontinued due to mild grade 1 eosinophilia (see the discussion on adverse effects, Section 3.2.3.2). In RM-493-012, one patient discontinued due to lack of efficacy, one due to protocol violation and one was lost to follow up for unknown reasons.

Overall, the ERG considered the omission of modelled treatment discontinuation may not be appropriate. Based on a review of liraglutide TA664[40], for managing overweight and obesity, a per cycle discontinuation rate was included in the model using evidence from the pivotal study 1839. Furthermore, based on clinical expert input to the ERG, it was highlighted that a small proportion of patients may discontinue treatment in clinical practice due to the burden of constant injections and/or adverse events (in particular skin pigmentation which may result from setmelanotide use). In order to explore uncertainty surrounding the impact of treatment discontinuation on cost effectiveness results, the ERG conducted a scenario analysis which implemented a treatment discontinuation rate of 1% per year throughout the lifetime horizon, for patients receiving setmelanotide who achieved maximum treatment effect (see Section 6.2.2). Based on clinical input to the ERG a 1% discontinuation rate was considered reasonable. This

analysis had a minor impact on results and it was incorporated into the ERG base case as it was deemed to represent a more realistic treatment pattern.

4.2.6.3. Mortality

Setmelanotide treated patients (responders)

Due the lack of trial-based mortality data, the company assumed that patients treated with setmelanotide can be expected to have a life expectancy comparable to individuals with general obesity of similar BMI levels. The company justified this based on setmelanotide trial-based treatment efficacy (which indicated a reduction in BMI) and clinical opinion. For adult patients, mortality was modelled based on a set of hazard ratios (HRs) stratified by BMI class from general obesity literature (Bhaskaran et al 2018[50]), which were then applied to background mortality for the general population derived from the UK life tables (Table 19). For paediatric patients, adult BMI mortality HRs were mapped to BMI Z-scores using a published algorithm by the World Health Organisation (WHO).

Given the large modelled incremental life year gain associated with setmelanotide compared to BSC, the ERG sought clinical input to validate the company's assumption that patients treated with setmelanotide can be expected to have a life expectancy comparable to individuals with general obesity of similar BMI levels. Clinical opinion to the ERG mentioned that individuals with POMC deficiency or PCSK1 mutation will be expected to suffer from hypoadrenalism and those with LEPR deficiency are more vulnerable to infections which increases their mortality risk. As such the company's base case assumption may not be appropriate. In the CS the company mentioned that the cause-specific mortality was not considered as POMC/PCSK1 and LEPR deficient patients usually experience multiple comorbidities, and the use of independent sources could potentially result in double-counting the mortality risk. The ERG considered this assumption to be broadly reasonable.

Due to the lack of long-term mortality data in patients treated with setmelanotide, the ERG conducted scenario analyses testing alternative mortality assumptions. These included a scenario which assumed no difference in mortality between responders and non-responders, as well as a scenario where non-responder and BSC life expectancies were converted to equivalent HR multipliers (see Table 24). The ERG considered this scenario to be extreme and highly exploratory. See Section 6.2.9 for results.

Table 24: BMI-based HRs for all-cause mortality (adult participants)

BMI	HR
20-25	1.00
25-30	1.21
30-35	1.42
35-40	1.63
40-45	1.84
45-50	2.05
≥50	2.26

Abbreviations: BMI, body mass index; HR, hazard ratio

BSC (non-responders)

The ERG noted that due to the rare nature of this condition, there is a lack of mortality data in patients with POMC/PCSK1 and LEPR i.e. basic epidemiological information for this condition is not available. Systematic literature reviews conducted by the company found no data surrounding the average lifespan of patients with POMC/PCSK1 and LEPR deficiency. As such, mean and maximum age life expectancy in the model was informed by clinical opinion to the company. These estimates were transformed into probability distribution functions and the company stated that a beta distribution was selected for both patients with POMC/PCSK1 and LEPR in the base case. The company did not provide a rationale for selecting the beta distribution. However, alternative distributions were available to select for use in the model i.e. Weibull and Log-logistic. The ERG noted that using these alterative distributions did not have a significant impact on results.

Due to the paucity of epidemiological data surrounding this condition, the ERG considered the company's estimates to be associated with some uncertainty. Clinical opinion to the ERG indicated that the company's estimate of maximum age life expectancy for POMC/PCSK1 and LEPR patients may be reasonable, however alternative values were suggested by one clinical expert (see Table 25). The ERG therefore conducted a scenario analyses using these alternative values (see Section 6.2.9 for results).

Table 25: Modelled mean and maximum age life expectancy (non-responders)

	POMC/PCSK1	LEPR
Mean age life expectancy (years)	[redacted]	[redacted]

	POMC/PCSK1	LEPR
Maximum age life expectancy (years)	[redacted]	[redacted]

Abbreviations: LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Additionally, the ERG did not agree with the company's use of alternative approaches to estimating mortality for responders and non-responders i.e. the lack of consistent methodology introduced further uncertainty. During clarification, the company provided justification for using different mortality approaches and updated the economic model to allow the user to estimate results using a HR approach for BSC and non-responder patients. The ERG considered this approach to be consistent with the approach for responders, however, there was a lack of transparency with respect to the derivation of HR multiplier. Following further clarification the company indicated that the value of HR multiplier has been calibrated using trial and error until a mean life expectancy was achieved in the model that was similar to the mean life expectancy estimates provided by clinical experts. The calibrated HR multipliers were [redacted] for POMC/PSCK1 and [redacted] for LEPR population. Though the ERG considered the explanation provided by the company to be reasonable, the approach taken was arbitrary and therefore uncertainty remained.

4.2.6.4. Adverse effects

The company did not include adverse events in the model and were asked to clarify their rationale during clarification (see A4). The company stated that these were not included gvien that grade 3 or 4 adverse events (which are normally considered in economic models) were not observed in the clinical trials. The ERG broadly agreed that grade 1 or 2 adverse events are not usually included in models. However certain (non-serious) adverse events, such as skin pigmentation could adversely impact patients HRQoL and may have an impact on cost effectiveness results.

The model accounted for certain co-morbidities, which were derived from clinical opinion to the company. These included sleep apnoea, osteoarthritis, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes and cardiovascular events. The company stated that a literature review was conducted to inform co-morbidity prevalence rates for patients with POMC/PCSK1 and LEPR, however no evidence was found. The company identified several studies which reported prevalence rates from morbidly obese patients who were eligible or considered for weight loss surgery. Due to the absence of relevant co-morbidity data, the company used these values as a proxy. These prevalence rates were not reported in the CS but were included in the

company's model. The ERG noted that the lack of relevant/generalisable co-morbidity prevalence data may be considered a source of uncertainty within the model, furthermore the company did not test uncertainty surrounding comorbidity prevalence rates via sensitivity analyses.

In addition, within the model, the same co-morbidity prevalence rates were applied to both adults and paediatric patients (apart from type 2 diabetes and cardiovascular events, which were excluded for paediatric patients based on clinical input to the company). The ERG considered the company's assumption of using equivalent co-morbidity prevalence rates in paediatric and adult patients to be a simplifying approach and not supported by sufficient rationale or clinical data. Furthermore, based on clinical input to the ERG, it is unreasonable to expect that paediatric patients will experience the same prevalence rates as adults, with respect to osteoarthritis and NAFLD. The ERG noted that this assumption potentially overestimates the HRQoL impact in paediatric patients. For completeness the ERG has conducted a scenario analysis which used lower co-morbidity prevalence rates for paediatric patients (see Section 6.2.9 for results).

In order to validate the company's list of modelled co-morbidities, clinical opinion to the ERG was sought. Based on clinical opinion to the ERG, the list appeared reasonable. The ERG noted that cancer (a potentially relevant co-morbidity) was not included within the model. The company justified the exclusion of cancer on the basis that most untreated LEPR and POMC/PCSK1 deficient patients die before they can develop the disease. Clinical opinion to the ERG broadly agreed with the company's assumption. However, it should be noted that based on the modelled effectiveness of setmelanotide, patients experience a considerable increase in life years compared to those receiving BSC i.e. there is a mortality benefit associated with treatment. As such it may be plausible for setmelanotide treated patients to develop cancer, as these patients live longer (based on modelled estimates).

4.2.6.5. Health-related quality of life

Impact on health-related quality of life

Patients with LEPR and POMC deficiency obesity continue to gain weight over the course of their lifetimes and QoL can be assumed to decrease in line with the increase in BMI. In addition, the QoL deficit related to hyperphagia remains throughout the course of the patient's life.

The company stated that limited trial data mean that no conclusions could be made regarding the impact of adverse events (AEs) on health-related quality of life (HRQOL). Clinical expert opinion noted the main AE to be hyperpigmentation, typically tolerated by most patients who as a result of their POMC and LEPR deficiencies are generally paler in complexion than the general population. Pigmentation generally increased initially before plateauing and was evenly distributed across the body. Other AEs were noted to be nausea and vomiting generally of mild intensity and transient. The ERG considered that the exclusion of modelled adverse event disutility, particularly with respect to hyperpigmentation, means that the analysis may not adequately capture all aspects relating to setmelanotide's impact on patient HRQoL.

It should be mentioned that carer disutility was not included in the model. The company stated that HRQoL data for carers were not available and so have not been included. In HST 14[39], metreleptin for the treatment of lipodystrophy, the ERG noted that a carer disutility was included and applied to the BSC arm only. Within this current appraisal, the ERG considered presenting a scenario analysis whereby carer disutility was applied to both setmelanotide and BSC arms, but results from this analysis did not indicate a meaningful impact. As such the scenario has not been presented. Overall, the inclusion of carer disutility was not considered to be a key driver of cost effectiveness.

Health state utility values

The model is built to capture the value of setmelanotide by considering its impact on the defective MC4R pathway and in turn having an effect on hyperphagia and BMI. Hyperphagia is thus treated as a condition within each BMI/BMI Z health state, with a resulting impact on QoL depending on severity. SF-36 data were collected in the pivotal studies but were not used in the analysis. The company noted a number of challenges using these data in the model: small sample size, lack of standardisation in timing of data collection, lack of generalisability to paediatric patients. In addition, the company noted that the SF-36 data recorded in the trial were likely to have captured some of the effect of hyperphagia on the quality of life of patients but did not account for it specifically. Overall, the ERG considered that the company's decision to exclude SF-36 data from the base case analysis was reasonable, given that the aforementioned limitations would likely lead to implausible or highly uncertain values.

Utility as a function of BMI

EQ-5D utilities for a general obesity population (based on the BMI and age from the broader literature) were used in the model (Table 26). The QoL in adults was derived from a published mapping to EQ-5D from SF-12 data.[43] The company noted a limitation of these data results from the lack of stratification of utility for BMI >50, which is relevant in the population of interest, and people with LEPR-deficiency in particular who are often immobile, relatively inactive, and have limited social interactions.[9] EQ-5D-based utilities in the paediatric population are informed by the PedsQL™ score reported in Riazi et al. [44] for BMI Z-score 0.0-1.0 and BMIz-score of 3.5-4.0. These values are then mapped from the PedsQL™ scale to EQ-5D[45]. EQ-5D utility values for the remaining BMI Z-score-based health states were then linearly extrapolated using the reported values (Table 27).

As no studies were identified in the company's SLR that provided utility values for the population of interest, utility values were sourced for the general obesity population. Given the absence of data for the population of interest, the ERG considered the approach taken by the company to be reasonable; however, it noted that no detail was provided in the CS as to how the studies that provided HRQoL input parameters for the model were identified.

Variation of utility score within each health state due to hyperphagia and/or comorbidities of obesity are accounted for by first applying a separate utility multiplier to each BMI or BMI Z-score health state weighted by the proportion of patients in each hyperphagia status (mild, moderate, or severe) as further described in next section, and then the disutility related to specific comorbidities are applied (in an additive manner), respectively.

Table 26: Modelled health state utility values (adult patients): EQ-5D utilities by BMI and age

BMI	Age							Reference
	18–30	31–40	41–50	51–60	61–70	71–80	81+	
20–25	0.91	0.89	0.86	0.83	0.81	0.79	0.79	Alsumali, 2018[43]
25–30	0.91	0.89	0.86	0.83	0.81	0.79	0.79	Alsumali, 2018[43]
30–35	0.89	0.86	0.82	0.80	0.79	0.76	0.76	Alsumali, 2018[43]
35–40	0.88	0.83	0.79	0.77	0.76	0.74	0.74	Alsumali, 2018[43]
40–45	0.84	0.82	0.75	0.73	0.71	0.69	0.69	Alsumali, 2018[43]
45–50	0.84	0.82	0.75	0.73	0.71	0.69	0.69	Alsumali, 2018[43]
>50	0.80	0.77	0.70	0.69	0.66	0.66	0.66	Alsumali, 2018[43]

Abbreviation: BMI, body mass index; EQ-5D, EuroQol 5 dimension

Source: CS, Document B, Table 71

Table 27. Modelled health state utility values (paediatric patients), mapped EQ-5D utility

BMI Z-score	Utility value	Reference	
	0.0-1.0	**0.89**	Rizazi et al., 2010[44]. Mapped PedsQL to EQ-5D based on Khan et al. 2014[45]
1.0-2.0	0.87	Linear extrapolation	
2.0-2.5	0.86	Linear extrapolation	
2.5-3.0	0.85	Linear extrapolation	
3.0-3.5	0.83	Linear extrapolation	
3.5-4.0	0.82	Riazi et al., 2010[44]. Mapped PedsQL to EQ-5D based on Khan et al. 2014[45]	
≥4.0	0.81	Linear extrapolation	

Abbreviation: BMI, body mass index; EQ-5D, EuroQol five dimension; PedsQL, Paediatric Quality of Life Inventory

Source: CS, Document B, Table 70

Disutility associated with hyperphagia

The impact on HRQoL due to hyperphagia was not directly assessed in the pivotal studies. The company therefore conducted a vignette study to estimate a modelled hyperphagia utility multiplier. The study was based on time trade-off (TTO) interviews with members of the UK general public. A total number 213 participants were included in the study and the interviews were conducted online. In order to define hyperphagia health states, the company sought input from clinical experts and reviewed published literature, this resulted in hyperphagia being categorised as no hyperphagia, mild hyperphagia, moderate hyperphagia and severe hyperphagia. The ERG was satisfied that the methodological approach used for the vignette study followed standard methods. Based on clinical input to the ERG, categorisation of hyperphagia according to the company's definitions versus clinical experience seemed to be reasonable.

The ERG noted that the company's vignette study and results were subject to uncertainty given that values were not elicited directly from patients with POMC/PCSK1 and LEPR, and therefore reliant on respondents' comprehension of the described health states, and ability to identify differences between health states based on the information provided in the vignette. Nevertheless, the ERG clinical expert confirmed that the vignettes were a plausible description of the degree of severity that would be observed in clinical practice. The main issue with the

vignettes is the degree of correspondence with the descriptions of health states used to obtain other hyperphagia related parameters; i.e. to inform the baseline severity distribution and transitions between severity levels (refer to the section on Modelled impact on hyperphagia in Section 4.2.6.1)

The ERG noted that the disutility due to hyperphagia was captured in the model using a utility multiplier based on the severity of hyperphagia experienced by an individual, independent of BMI or age, consistent with established methodology (Ara and Brazier, 2010)[46]. These multiplier values, obtained from the company's vignette study, are shown in Table 28. Also, in the model hyperphagia transitions are captured within the utility multiplier itself by weighting the multiplier according to the proportion of patients in the mild, moderate and severe hyperphagia status: for cycle 0, it is weighted based on the baseline hyperphagia status distribution and for cycle 1 and beyond, it is based on the proportion of patients in the mild, moderate and severe hyperphagia status at the end of cycle 1. While the ERG did not consider this approach to be unreasonable, it noted the difference in approach versus the application for each of the comorbidities for which disutilities were implemented in an additive manner. No justification was provided for the choice of the multiplicative approach over the additive approach, however, the ERG noted that both approaches, when considered at the same level, are likely to lead to similar results and therefore did not consider this to be a key concern.

Table 28: Hyperphagia utility multiplier

Hyperphagia Status	Multiplier	Reference
Mild	[redacted]	Vignette study
Moderate	[redacted]	Vignette study
Severe	[redacted]	Vignette study

Source: CS, Document B, Table 72

Although clinical advice to the ERG suggested that the descriptions of mild, moderate and severe hyperphagia were appropriately reflective of patient experience and the methods of the vignette study were appropriate, the ERG noted that the utility loss associated with moving from moderate to severe hyperphagia ([redacted]) was considerably higher than moving from mild to moderate hyperphagia ([redacted]). The company did not comment on the reasonableness of these estimates or attempt to validate these values.

Furthermore, the ERG was aware that the company's approach to modelling hyperphagia disutility differed to an approach used previously in metreleptin HST 14[39] for the treatment of

lipodystrophy, whereby a utility decrement (−0.11) was modelled based on the presence of hyperphagia (not stratified according to mild, moderate and severe). The company justified their severity-based approach on the basis that it better quantified the impact on quality of life based on the severity of hyperphagia experienced. Whilst there is some uncertainty surrounding the utility values derived from the vignette study, the ERG broadly agreed with the company's approach to categorise hyperphagia according to severity. As part of a combined scenario analysis addressing uncertainty surrounding hyperphagia modelled inputs, the ERG assumed that mild hyperphagia would reflect the value reported in metreleptin HST 14[39] for hyperphagia presence (−0.11), whilst the values for moderate and severe would be twice (−0.22) and three times (−0.33) this value, respectively. The ERG acknowledged the limitations surrounding this assumption-based approach and considered this analysis to be exploratory in nature. Refer to Section 6.2.5 for further details and results.

Disutilities associated with comorbidities

Disutility due to AEs was not included in the analysis due to the lack of availability of data in the setmelanotide trials.

The model considered the following comorbidities: sleep apnoea, osteoarthritis, NAFLD, T2DM, and cardiovascular events (refer to Section 4.2.6.4). For each comorbidity, a mean disutility was applied on top of the utility multiplier for hyperphagia. Disutilities for comorbidities were implemented in an additive manner in accordance with established methodology (Ara and Brazier 2010)[46].

The company used Soltoft et al (2009)[51] to derive disutilities for sleep apnoea, osteoarthritis and type 2 diabetes, and Sullivan et al (2011)[52] to derive disutilities for cardiovascular events. Although these studies are referenced in Section 10.1.6 of the CS, the ERG was unclear as to how these studies were identified by the company. The EQ-5D disutility values reported in Søltoft et al (2009)[51] and Sullivan et al (2011)[52] based on surveys of general population adults in UK and USA respectively. However, the EQ-5D utility scores reported in the catalogue developed by Sullivan et al. (2011)[52] are based on US community preferences and not on the UK community preferences. The ERG noted that in HST 14[39], sources for CV disutilities included the UK Prospective Diabetes Study (UKPDS), as well as TA288[53] and TA390[54]. As such, more generalisable sources appeared to have been available for use. The company stated that no evidence was identified from which disutilities could be derived for NAFLD. Clinical opinion to the company indicated that the utility for NAFLD to be similar to that for

obesity and hence no added disutility was assumed. Disutilities used in the analysis are provided in Table 29.

Table 29. Summary of disutilities for comorbidities

Disutility due to:	Utility value	Reference	Justification provided
Sleep apnoea	0.034	Søltoft et al. (2009)[51]	Based on the association between obesity and respiratory problems (which were assumed to reflect obstructive sleep apnoea). Average of utility decrements by sex were used
Osteoarthritis	0.187	Søltoft et al. (2009)[51]	Based on association between musculoskeletal problems and HRQoL. Average of utility decrements by sex were used
NAFLD	0.000	No evidence available.	No added disutility assumed. Assumption based on the suggestion NAFLD GDG[55] to consider utility for NAFLD similar to patients with obesity
T2DM	0.043	Søltoft et al. (2009[51]	Based on association between T2DM and HRQoL. Average of utility decrements by sex were used
CV events	0.064	Sullivan et al. (2011)[52]	Weighted average of HRQoL decrements based on the CV event type and proportion of each CV event type

Abbreviations: CV, cardiovascular; GDG, guideline development group; HRQoL, health-related quality of life; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Source: CS, Document B, Table 64

Given that prevalence rates and disutilities were not derived directly from patients with POMC/PCSK1 and LEPR, the ERG conducted scenario analyses to explore the impact of uncertainty in respect of the prevalence and disutilities associated with comorbidities (refer to Section 6.2.7).

4.2.6.6. Resources and costs

Treatment and administration costs

Treatment acquisition costs were included for setmelanotide, which is a solution for injection available in a 10 mg/ml vial (each vial contains 10 mg of setmelanotide in 1 ml solution for injection). The company did not provide the cost per 10 mg/mL vial; however, noted the list price

to be [redacted] per mg. The ERG acknowledged that this equates to a cost of [redacted] per vial. The company's approach to estimating treatment costs in the model was based on an averaging approach whereby the total dose from the pivotal studies RM-493-012 and RM-493-015 was divided by the number of patients. Based on this approach the average setmelanotide dose in Year 1 was [redacted] and [redacted] in Years 2+. Based on these dosing estimates, setmelanotide resulted in an annual treatment cost per patient of [redacted] in Year 1 and [redacted] in Years 2+.

The ERG noted that the company's base case approach to estimating treatment costs does not reflect potential differences in dosing requirements between paediatric and adult patients and therefore does not accurately depict treatment costs for these distinct patient populations. During clarification, the company was asked to provide the average dose separately for adults and patients in the pivotal studies. The company subsequently updated the economic model to allow the user to estimate treatment cost according based on this stratified approach.

For BSC, the model did not include any treatment acquisition costs. The ERG considered this to be reasonable given that the comparator was dietary advice and exercise. Administration costs in both treatment arms were estimated to be £0. The company justified the omission of administration costs in the setmelanotide arm on the basis that patients self-inject treatment. As noted previously adverse events were not included in the model, therefore associated costs were not included.

Health state, monitoring and comorbidity costs

Setmelanotide is given in addition to BSC (obesity management costs, which included dietary and exercise advice). All BMI and BMI Z health states were therefore associated with BSC background costs. The company estimated the mean cost of obesity management to be £140.82 in the model and stated that this was based on Personal Social Services Research Unit (PSSRU) and NHS reference costs from 2012, 2017 and 2018, which were inflated to the 2021 values. Although the ERG considered the source to be reasonable, the ERG was unable to identify the cost selected by the company in the PSSRU. It was therefore unclear whether the cost reflected GP, nurse, or consultant time (and the quantity of time). The company did conduct one-way sensitivity analysis (OWSA) which varied the cost of BSC by +/- 20%, results were not overly sensitive to this.

As a scenario analysis the company estimated BSC health state costs according to BMI class (as opposed to a mean cost). This was a somewhat simplistic approach whereby the mean cost

was assumed to be representative of the lowest BMI class 20–25 (or BMI Z of 0.0–1.0), and £25 was added for each increased BMI class/ BMI Z-score. The ERG noted that estimating BSC costs based on BMI class did not have an impact on the results.

Annual monitoring costs were included in the model for both setmelanotide + BSC and BSC treatment arms. These included full blood count and liver function tests, comprehensive metabolic panel and physician visits. The ERG identified that there was a notable difference in the frequency of annual physician visits between treatment arms i.e. the number of physician visits per annum was assumed to be one for setmelanotide and four for BSC patients. The company stated that frequency of monitoring was based on clinical expert opinion. Based on clinical input to the ERG, the number physician visits for setmelanotide treated patient appeared to be slightly underestimated. The company did vary monitoring costs by +/− 20% in their OWSA, however this did not have an impact on results.

The model included annual management costs for comorbidities including sleep apnoea, osteoarthritis, NAFLD, type 2 diabetes and cardiovascular events. Costs were taken from a range of published literature sources including McMillan et al 2015[56] and Younossi et al 2016[57]. The ERG noted that the cost of acute cardiovascular events were not included in the model. The company conducted a scenario analysis which included acute cardiovascular event costs, however results were not sensitive to this.

5. COMPANY'S COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Company base case

The results for the LEPR, POMC and overall population were reported by the company and are shown in Table 30. Based on this analysis, setmelanotide resulted in a base case deterministic ICERs of £169,147, £189,215 and £176,913 compared to BSC in the LEPR, POMC and overall populations respectively. The ERG noted that the ICER for the overall population is simply based on a weighted average of the LEPR and POMC ICERs. As noted previously, the ERG do not consider the overall analysis to be appropriate for decision making as results varied and should be presented according to disease type (LEPR or POMC) and patient age (paediatric or adult).

Table 30: Company base case results (LEPR, POMC and overall population)

	Total Costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYG	Cost per QALY gained
	Company deterministic base case						
Setmelanotide + BSC (LEPR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,147
BSC (LEPR)	£25,233	2.73	12.01	-	-	-	-
Setmelanotide + BSC (POMC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£189,215
BSC (POMC)	£40,903	6.35	21.77	-	-	-	-
Setmelanotide + BSC (Overall)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,913 (weighted average)
BSC (Overall)	£30,451	3.94	15.26	-	-	-	-
	Company probabilistic base case						
Setmelanotide + BSC (Overall)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£177,712 (weighted average)
BSC (Overall)	£30,388	3.95	15.30	-	-	-	

Abbreviations: BSC, best supportive care; LEPR, leptin receptor; LYG, life years gained; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

5.1.2. Subgroup analyses results

The company conducted subgroup analyses, exploring the impact in four specific subgroups: paediatric individuals with LEPR deficiency, adult individuals with LEPR deficiency, paediatric individuals with POMC/PCSK1 deficiency, and adult individuals with POMC/PCSK1 deficiency.

Based on these analyses, setmelanotide resulted in a base case deterministic ICER of £165,424, compared to BSC in paediatric with LEPR deficiency, with the incremental costs and QALYs of [redacted] and [redacted], respectively. The deterministic and the probabilistic base case results are presented below in Table 31. Please note that the probabilistic analysis for the subgroups were run by the ERG, as it was not been provided in the company submission.

Table 31: Subgroup analysis results (LEPR paediatric)

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYG	Cost per QALY gained
	Company deterministic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,424
BSC	£28,089	3.30	14.21	-	-	-	-
	Company probabilistic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,980
BSC	£27,843	3.30	14.20	-	-	-	-

Abbreviations: BSC, best supportive care; LEPR, leptin receptor; LYG, life years gained; QALYs, quality-adjusted life years

For adults with LEPR deficiency, setmelanotide resulted in a base case deterministic ICER of £181,769 compared with BSC, with the incremental costs and QALYs of [redacted] and [redacted], respectively.

The deterministic and the probabilistic base case results are presented below in Table 32.

Table 32: Subgroup analysis results (LEPR adult)

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYG	Cost per QALY gained
	Company deterministic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£181,769
BSC	£17,103	1.12	5.75	-	-	-	-
	Company probabilistic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,886
BSC	£17,979	1.20	6.12	-	-	-	-

Abbreviations: BSC, best supportive care; LEPR, leptin receptor; LYG, life years gained; QALYs, quality-adjusted life years

For paediatric individuals with POMC/PCSK1 deficiency, setmelanotide resulted in a base case deterministic ICER of £191,348, compared with BSC with the incremental costs and QALYs of [redacted] and [redacted], respectively. The deterministic and the probabilistic base case results are presented below in Table 33.

Table 33: Subgroup analysis results (POMC paediatric)

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYG	Cost per QALY gained
	Company deterministic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£191,348
BSC	£43,104	7.03	23.86	-	-	-	-
	Company probabilistic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£191,012
BSC	£42,589	6.92	23.57	-	-	-	-

Abbreviations: BSC, best supportive care; LYG, life years gained; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

For adult individuals with POMC/PCSK1 deficiency, setmelanotide resulted in a base case deterministic ICER of £183,100, compared with BSC with the incremental costs and QALYs of [redacted] and [redacted], respectively. The deterministic and the probabilistic base case results are presented below in Table 34.

Table 34: Subgroup analysis results (POMC adult)

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	Incremental LYG	Cost per QALY gained
	Company deterministic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,100
BSC	£34,638	4.43	15.82	-	-	-	-
	Company probabilistic base case						
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,198
BSC	£34,095	4.35	15.63	-	-	-	-

Abbreviations: BSC, best supportive care; LYG, life years gained; POMC, proopiomelanocortin; QALYs, quality-adjusted life years

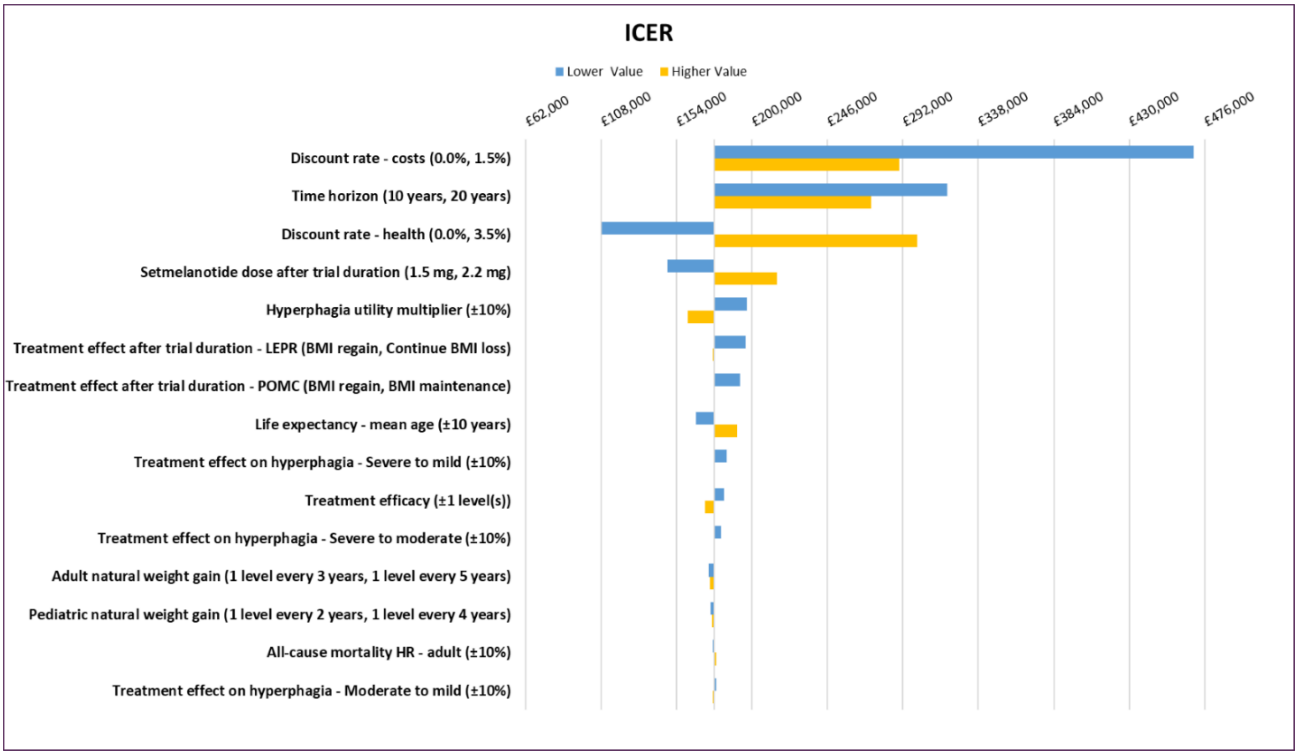
5.1.3. Company's sensitivity analyses

The company undertook OWSA, probabilistic sensitivity analysis (PSA) and additional scenario analyses. A key limitation relating to the company's PSA sensitivity analysis is the omission of treatment effectiveness and other key variables as tested parameters. As setmelanotide treatment effect is considered a key driver of QALYs within this appraisal, the ERG consider the company's PSA to be limited and does not adequately capture uncertainty.

5.1.3.1. One-way sensitivity analysis

The company conducted OWSA whereby key model parameters were varied arbitrarily to determine the impact on the base case ICER. Based these results, the ICER was most sensitive to variation in the discount rate for costs (0% and 1.5%) and benefits (0% and 3,5%), a reduced time horizon (10 years, 20 years), [redacted] and hyperphagia utility multiplier (+/- 10%). Results are displayed in Figure 2.

Figure 2: Tornado diagram of one-way sensitivity analysis results



Abbreviations: BMI, body mass index; HR, hazard ratio; ICER, incremental cost-effectiveness ratio(s); POMC, proopiomelanocortin

5.1.3.2. Probabilistic sensitivity analyses

The company conducted probabilistic sensitivity analysis, which tested a number of model parameters simultaneously and was run for 1000 iterations. Based on this analysis, setmelanotide + BSC was associated with a probabilistic ICER of £177,712 (a scatterplot of incremental costs vs incremental QALYs has been shown in Figure 3). At a willingness to pay (WTP) threshold of £100,000 per QALY, the probability for setmelanotide to be cost-effective is 0% while it increases to 3% at £150,000 per QALY and 85% at £200,000 per QALY (as per the CEAC shown in Figure 4).

The ERG noted the following concerns surrounding the company's handling of the PSA within this appraisal.

- The PSA did not test the parameters mentioned below (Table 35) and the company did not provide any rationale for excluding these. Therefore the company's submitted model does not appear to have appropriately assessed the uncertainty. Further, given that the

ERG did not have access to the relevant individual patient data to inform distributions for these parameters, it was not possible to re-run the PSA including these parameters.

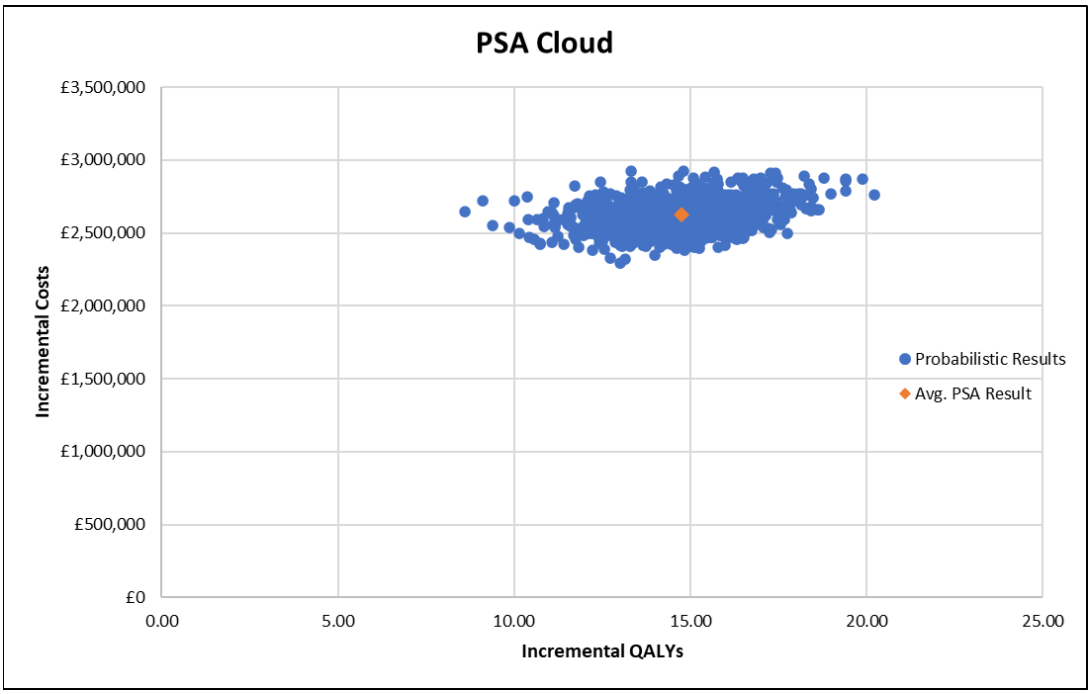
Table 35. Model parameters which were not included in the PSA

S. No	List of parameters not included in the PSA
1	**Baseline characteristics related parameters:** Mean age, % Female, Baseline BMI distribution for paediatric and adults, baseline hyperphagia distribution
2	**Natural weight gain (BSC):** Natural weight gain – Increase BMI class by (levels) and Natural weight gain – Increase BMI class in (years)
3	**Treatment efficacy related parameters:** Response rate by BMI (for both paediatric and adults), Overall treatment effect in year 1 (for both paediatric and adults), treatment effect by BMI in year 1 (for both paediatric and adults), Treatment effect after trial duration, Drop BMI class by (levels), Drop BMI class in (years)
4	**Mortality:** HR multiplier for non-responders
5	**Costs:** Setmelanotide dosing (for both paediatric and adults) and the treatment costs

Abbreviations: BMI, body mass index; BSC, best supportive care; HR, hazard ratio; PSA, probabilistic sensitivity analysis

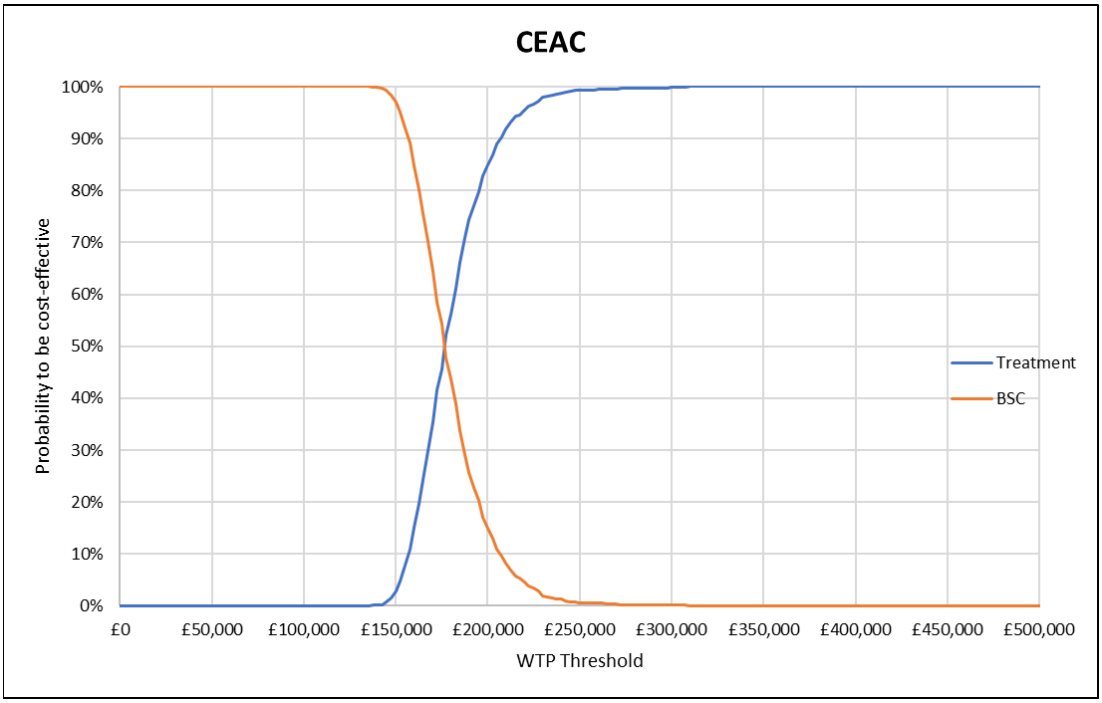
- Within the cost-effectiveness acceptability curve (CEAC) it was noted the maximum willingness to pay to be £500,000. However, within the interim process and highly specialised technologies programme, it specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources.

Figure 3: PSA scatter plot



Abbreviations: PSA, probabilistic sensitivity analysis; QALY quality-adjusted life year

Figure 4: CEAC



Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; WTP, willingness to pay

5.1.3.3. Scenario analyses

The company conducted the scenario analyses summarised in Table 36 for the overall population only. The results of these analyses are shown in Table 37. The ERG noted that results were most sensitive to scenarios which tested alternative hyperphagia assumptions, i.e. scenarios 4 and 8.

Table 36: Company scenario analyses

Scenario	Description
Scenario 1	Uniform baseline BMI distribution
Scenario 2	Distribution of POMC and LEPR based on trial population
Scenario 3	Distribution of paediatric and adults based on trial population
Scenario 4	All responders have 1 level of improvement in hyperphagia
Scenario 5	Inclusion of only co-morbidities that are prevalent in paediatric patients
Scenario 6	Incremental cost of BSC by BMI
Scenario 7	Response rate stratified by age group based on trial
Scenario 8	Hyperphagia mapping based on worst hunger score
Scenario 9	Increased co-morbidity disutility by 50%
Scenario 10	Account for acute costs of CV events
Scenario 11	Utility scores decreased by 0.05 for BMI ≥ 50

Abbreviations: BMI, body mass index; BSC, best supportive care; CV, cardiovascular; LEPR, leptin receptor; POMC, proopiomelanocortin

Table 37: Company scenario analysis results (based on overall population)

Scenario	Incremental life years	Incremental QALYs	Incremental costs	Cost per QALY gained
Scenario 1	[redacted]	[redacted]	[redacted]	£173,856
Scenario 2	[redacted]	[redacted]	[redacted]	£180,010
Scenario 3	[redacted]	[redacted]	[redacted]	£178,696
Scenario 4	[redacted]	[redacted]	[redacted]	£191,812
Scenario 5	[redacted]	[redacted]	[redacted]	£176,697
Scenario 6	[redacted]	[redacted]	[redacted]	£176,906
Scenario 7	[redacted]	[redacted]	[redacted]	£177,015
Scenario 8	[redacted]	[redacted]	[redacted]	£224,778
Scenario 9	[redacted]	[redacted]	[redacted]	£177,134

Scenario	Incremental life years	Incremental QALYs	Incremental costs	Cost per QALY gained
Scenario 10	[redacted]	[redacted]	[redacted]	£176,929
Scenario 11	[redacted]	[redacted]	[redacted]	£176,708

Abbreviation: QALY, quality-adjusted life year

5.1.4. Model validation and face validity check

In the Section 12.7 of the CS, the company has indicated that the model was internally validated, and the expert opinion was sought in specific instances (e.g., treated, and untreated lifespan estimates / mortality). However, the CS did not provide the quality checklist used to assess the model via a series of validation checks. Nevertheless, ERG was able to replicate the deterministic base case, deterministic sensitivity analyses (DSA) and PSA results using the model submitted by the company.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified several limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the ERG believes are more plausible.

This section is organised as follows:

- Section 6.1 details the impact of errors identified in the ERG's validation of the company's model.
- Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the company corrected base-case analysis. The scenario analyses presented in Section 6.2, focus on exploring the key issues and uncertainties around the company's base case assumptions.
- Section 6.3 presents the ERG base-case based on a combination of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

The company resolved the identified error regarding the hyperphagia related treatment effect assumption in response to the ERG clarification question B11 and provided an updated model as mentioned in Section 4.2.6.1. Table 38 provides the deterministic and probabilistic results for the corrected company's base case i.e., for the overall population.

The ERG corrected company base case results for the individual subgroups are presented in Section 6.3.

Table 38: ERG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Setmelanotide + BSC (Overall)	[redacted]	[redacted]	[redacted]	[redacted]	£178,488 (weighted average)
BSC (Overall)	£30,451	3.94	-	-	-

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company probabilistic base case					
Setmelanotide + BSC (Overall)	[redacted]	[redacted]	[redacted]	[redacted]	£179,286 (weighted average)
BSC (Overall)	£30,388	3.95	-	-	-

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; QALY, quality-adjusted life year

Though the ERG identified that some of the key model parameters were not included in the PSA (as mentioned in Section 5.1.3.2), it was not possible to re-run the PSA without the necessary data to inform relevant distributions and hence the impact of including those parameters in the PSA remains unexplored.

6.2. Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted scenario analyses for the key uncertainties outlined in Section 4. It should be noted that the ERG preferred results to be presented according to subgroups, that is LEPR paediatric, LEPR adult, POMC paediatric and POMC adult. Therefore, the results for four sets of scenario analyses were produced (see Section 6.2.9).

6.2.1. Scenario 1: Modelled treatment effectiveness

Due to the lack of robust comparative clinical data and absence of long-term effectiveness data, the ERG considered there to be significant uncertainty surrounding the company's approach to modelling treatment effectiveness. As such the following scenarios explore the impact of using alternative effectiveness assumptions.

- In Scenario 1a) an alternative treatment efficacy assumption (beyond the trial duration) was explored. In this regard, the BMI regain option within the company's model was used for both POMC and LEPR populations. This scenario assumed that weight regain occurred after three years and BMI class increased by [redacted] every four years.
- Scenario 1b), which assumed that BMI is maintained after the trial duration, applies to POMC patients only, as the company had already assumed BMI [redacted]. These scenarios had a moderate upward impact on ICER. See Section 6.2.9 for results.

- In Scenario 1c) modelled treatment response rates are based on BMI class (as opposed to using an overall rate in the model for POMC and LEPR, estimated to be 86% and 60% respectively). This approach does not have a significant impact on the ICER, however the ERG noted that this is more consistent with the modelling approach used by the company, which stratifies health states according to BMI class. Due to the small patient numbers, lack of patients in certain BMI cases at baseline and uncertainty surrounding this scenario analysis, the ERG did not consider BMI class response rates as part of the ERG base case. See Section 6.2.9 for results.
- In Scenario 1d) BMI is assumed to drop by [redacted] for patients with POMC and [redacted] for patients with LEPR (as opposed to [redacted] for patients with POMC and [redacted] for patients with LEPR), for the trial period. Due to the uncertainties outlined in Section 4.2.6 and the lack of long-term data supporting the company's base case assumption, the ERG considered it reasonable to test a lower treatment effectiveness assumption in both populations. This scenario had a moderate upward impact on the ICER. See Section 6.2.9 for results.

6.2.2. Scenario 2: Treatment discontinuation

As mentioned in Section 4.2.6.2, treatment discontinuation was not considered in the model. This did not align with the clinical trial results or clinical opinion. To test the impact of introducing treatment discontinuation into the model, the ERG ran a scenario assuming 1% discontinuation rate per year throughout the lifetime horizon.

The ERG made the following assumptions in this scenario:

- Treatment discontinuation has been considered only for responders alongside the response evaluation at 12 weeks.
- Upon discontinuation, patients were assumed to move to their respective health states in the non-responder arm. Non-responders in the intervention arm receive BSC and so the treatment acquisition costs, hyperphagia utility distribution and survival rates are the same as BSC.
- The discontinuation rate of 1% was applied only to one health state (rather than from all health states patients enter the model), where a higher proportion of cohort spend their time in the lifetime model. For adults, this was found to be the 30-35 BMI and 40-45 BMI health

states for POMC and LEPR, respectively. For paediatric patients, it was 2.0-2.5 BMI Z-score and 2.5-3.0 BMI Z-score-based health states for POMC and LEPR, respectively. It should also be noted that once paediatric patients reach adulthood, they transition to their respective adult BMI based health states (that their BMI Z-score-based health states were mapped to). This assumption was necessary to reduce the complexity of following cohorts of patients who discontinued across multiple health states through the model.

This scenario has been considered in the ERG base case. Results were not overly sensitive to this analysis, see Section 6.2.9 for results.

6.2.3. Scenario 3: Discount rate for health outcomes

As mentioned in Section 4.2.5, the company has used a 1.5% discount rate for health outcomes citing the increased life expectancy associated with setmelanotide. However, given that mortality gains are strictly modelled and was not directly derived from the trials, the ERG considered it appropriate to use a 3.5% discount rate for health outcomes, reflective of NICE reference case discounting. This scenario has been considered in the ERG base case and it had a considerable impact on the ICER. See Section 6.2.9 for results.

6.2.4. Scenario 4: Mortality

The lack of availability of mortality data in patients with POMC/PCSK1 and LEPR was identified as a key area of uncertainty within this appraisal. The ERG conducted the following scenario analyses to assess the impact of alternative mortality assumptions on the ICER.

- In scenario 4a) it was assumed that responders would not experience a mortality benefit. The ERG conducted this analysis due to the paucity of available mortality data from clinical studies and published literature; however, it is considered an extreme scenario, as it is not supported by clinical opinion or aligned with clinical effectiveness evidence. Results were sensitive to this analysis. See Section 6.2.9 for results.

- In scenario 4b) non-responder and BSC life expectancy were converted to equivalent HR multipliers. As noted in Section 4.2.6.3, the ERG regarded that the company's approach to estimating mortality for responders and for non-responders was inconsistent. During clarification, the company revised their model which enabled mortality life expectancy estimates for non-responders (based on clinical opinion) to be converted to an equivalent

hazard ratio multiplier, in order to ensure a consistent approach as explained in Section 4.2.6.3. Results were not very sensitive to this analysis. See Section 6.2.9 for results.

- In scenario 4c) the company's mortality multiplier for non-responders and BSC was decreased by 10%. Due to the uncertainty surrounding the company's methodology with respect to the conversion of life expectancy estimates to an equivalent HR multiplier, the ERG conducted this scenario analysis which reduced the severity of the non-responder/BSC mortality multiplier by an arbitrary value of 10%. Results were not very sensitive to this analysis. See Section 6.2.9 for results.
- In scenario 4d) the mean and maximum age life expectancy for non-responders and BSC was varied based on clinical opinion to ERG. The mean and maximum age life expectancy based on clinical opinion to ERG are given in Table 39 below. An upward impact on the ICER was noticed in this scenario for the LEPR population. See Section 6.2.9 for results.

Table 39. Mean and maximum age life expectancy based on clinical opinion to ERG

	POMC/PCSK1	LEPR
Mean age life expectancy (years)	45	50
Maximum age life expectancy (years)	55	60

Abbreviations: ER|G, Evidence Review Group; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

6.2.5. Scenario 5: Combined scenario analysis on hyperphagia related model inputs

As mentioned in Section 4.2.6.5, the ERG conducted a combined scenario analysis to explore uncertainty surrounding the data related to hyperphagia used in the model. The following parameters related to hyperphagia were altered using a stacked approach as mentioned below.

- Firstly, the company's baseline hyperphagia status distribution was altered as per clinical opinion to ERG, described in Table 40 below.

Table 40: Hyperphagia baseline distributions for scenario analysis

	POMC: Company	POMC: ERG	LEPR: Company	LEPR: ERG
Mild	[redacted]	10%	[redacted]	0%
Moderate	[redacted]	40%	[redacted]	0%
Severe	[redacted]	50%	[redacted]	100%

Abbreviations: ERG, Evidence Review Group; LEPR, leptin receptor; POMC, proopiomelanocortin

- Secondly, with respect to the impact of treatment on hyperphagia (i.e. hyperphagia health state transition probabilities), the ERG noted that transition probabilities were based on an internal analysis by the company and details were not provided in in the CS. Given that the company's method was not transparent and due to the lack of direct trial data supporting the impact of setmelanotide on hyperphagia severity, the ERG opted to reduce the impact of setmelanotide on hyperphagia (transition probability matrices are presented in Table 41). For POMC it was assumed the proportion of patients moving from severe to mild hyperphagia would be 33.3% vs [redacted] in the company base case, whilst for LEPR it was assumed the proportion of patients moving from moderate to mild hyperphagia to be 50% vs [redacted] in the company base case for LEPR patients. These transition probabilities were arbitrarily selected by the ERG in the absence of alternative robust data sources.

Table 41: Hyperphagia transition probability matrices for scenario analysis

	LEPR: company matrix			LEPR: ERG matrix		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Mild	[redacted]	[redacted]	[redacted]	100.0%	50.0%	50.0%
Moderate	[redacted]	[redacted]	[redacted]	0%	50.0%	50.0%
Severe	[redacted]	[redacted]	[redacted]	0%	0%	0%
	POMC: company matrix			**POMC: ERG matrix**		
Mild	[redacted]	[redacted]	[redacted]	100%	40%	33.3%
Moderate	[redacted]	[redacted]	[redacted]	0%	60%	66.7%
Severe	[redacted]	[redacted]	[redacted]	0%	0%	0%

Abbreviations: ERG, evidence review group; LEPR, leptin receptor; POMC, proopiomelanocortin

- Thirdly, to explore the uncertainly surrounding the utility multiplier used by the company for hyperphagia, alternative utility multipliers were derived based on the disutility estimates for hyperphagia from metreleptin HST 14[39] (see Table 42). It should be noted that utility values in HST 14 were not presented according to hyperphagia severity, therefore the value presented in the appraisal i.e. -0.11, was considered for mild (as the value derived using a discrete choice experiment was considered an underestimate by ERG in the HST 14[39]) and the values for moderate and severe hyperphagia were assumed to be twice (-0.22) and three times (-0.33) that of mild, respectively. As the impact of hyperphagia related utility had been modelled as multipliers in the model, the disutilities were transformed into equivalent

utility multipliers. Given a baseline utility of 1, applying a disutility of -0.11 is the same as applying a utility multiplier of 0.89, in theory. However, as baseline patients are unlikely to be in full health a baseline utility of 0.9 was assumed (which is close to the adult health state utility with the BMI of 25-30 in the 18-30 age group (0.91) used in the model) and the utility multiplier derived subsequently are given below.

Table 42. Alternative hyperphagia utility multiplier based on metreleptin appraisal[39]

Hyperphagia Status	Disutility (as per metreleptin HST 14[39])	Equivalent Multiplier (baseline utility = 0.9)
Mild	-0.11	0.801
Moderate	-0.22	0.702
Severe	-0.33	0.603

Abbreviations: HST, highly specialised technology

This combined scenario had a significant upward impact on the ICER. See Section 6.2.9 for results.

6.2.6. Scenario 6: Time horizon

As outlined in Section 4.2.5, the ERG considered the company's base case time horizon to be reasonable. However, to determine the impact of a shorter time horizon, whereby costs and benefits are truncated at an earlier time point, this scenario reduces the time horizon to 20 years. Results are extremely sensitive to this analysis See Section 6.2.9.

6.2.7. Scenario 7: Prevalence rates and disutilities for comorbidities decreased by 10%

Due to the lack of data in patients with POMC and LEPR comorbidity prevalence rates used by the company in the base case were derived from published literature sources which included either obese or morbidly obese patients. The ERG acknowledged the scarcity of relevant co-morbidity data for the population of interest and the agreed that the company's use of general obesity data to inform co-morbidities may serve as a reasonable proxy (albeit there were some concerns surrounding the generalisability of these data as noted in Sections 4.2.6.4 and 4.2.6.5). Furthermore, the same co-morbidity prevalence rates were applied to both adults and paediatric patients (apart from T2DM and cardiovascular events, which were excluded for paediatric patients based on clinical input to the company). Based on clinician input to the ERG, it was noted that the company's base case assumption may not be appropriate, as adults would

be expected to have higher prevalence rates for NAFLD and osteoarthritis. In order to explore uncertainty surrounding modelled comorbidities, the ERG conducted the following scenario analyses;

- Scenario 7a) Prevalence rates and disutilities decreased by 10% (both adults and paediatric patients). Results were not sensitive to this analysis, see Section 6.2.9.
- Scenario 7b) Paediatric patients assumed to have 10% lower prevalence rates with respect to NAFLD and osteoarthritis, than adults (based on clinical opinion to ERG). Disutilities were also decreased by 10%. Results were not sensitive to this analysis, see Section 6.2.9 for results.

6.2.8. Scenario 8: Stratified dosing for setmelanotide

The setmelanotide trials indicated that the dosing for paediatric and adults are different, however, the company has used an average dosing for both paediatric and adults in the original model. Upon clarification (clarification question B4), the company updated the model with separate dosing for paediatric and adults as per the trials. This scenario tested impact of the alternative stratified dosing on the results. Results were sensitive to this analysis and formed part of the ERG base case. See Section 6.2.9 for results.

6.2.9. Exploratory analyses: impact on the ICER

The ERG has made the changes described in Sections 6.2.1 to 6.2.8. Each change has been made individually except for the combined scenarios. The results of the ERG's exploratory analyses are provided in Table 43 to Table 46, by subgroup (LEPR, paediatric; LEPR, adult; POMC, paediatric; POMC, adult).

Table 43: Exploratory analyses undertaken by the ERG (LEPR, paediatric)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from ERG corrected company base case
ERG corrected company base-case (LEPR, paediatric)		[redacted]	[redacted]	£166,843	-
Scenario 1: Modelled treatment effectiveness					
a) Alternative treatment efficacy assumption after trial duration (BMI regain)		[redacted]	[redacted]	£193,008	16%

b) Alternative treatment efficacy assumption after trial duration (BMI maintenance)		Not applicable for LEPR			
c) Treatment response rates based on BMI class		[redacted]	[redacted]	£165,424	-1%
d) Reduced setmelanotide efficacy during trial period (BMI drops by [redacted] for LEPR)		[redacted]	[redacted]	£174,282	4%
Scenario 2: 1% discontinuation rate per year throughout the lifetime horizon		[redacted]	[redacted]	£181,001	8%
Scenario 3: 3.5% discount rate for health outcomes		[redacted]	[redacted]	£289,996	74%
Scenario 4: Mortality					
a) No mortality benefit for responders		[redacted]	[redacted]	£220,766	32%
b) Non-responder and BSC life expectancy converted to equivalent HR multiplier		[redacted]	[redacted]	£166,446	0%
c) Company's base case mortality multiplier for non-responders and BSC decreased by 10%		[redacted]	[redacted]	£167,543	0%
d) Increased mean and maximum age life expectancy for non-responders and BSC (based on clinical opinion to ERG)		[redacted]	[redacted]	£191,660	15%
Scenario 5: Combined Hyperphagia scenario					
Alternative baseline distribution + transition probability (moderate to mild: 50% + disutility based on metreleptin appraisal (equivalent utility multiplier)		[redacted]	[redacted]	£215,536	29%
Scenario 6: 20-year time horizon		[redacted]	[redacted]	£266,793	60%

Scenario 7: Co-morbidity prevalence rates and disutility reduced					
a) Prevalence rates and disutilities decreased by 10%		[redacted]	[redacted]	£166,587	0%
b) Paediatric patients assumed to have 10% lower prevalence rates and disutility compared to adults.		[redacted]	[redacted]	£166,887	0%
Scenario 8: Setmelanotide dosing separately for paediatric and adults		[redacted]	[redacted]	£215,295	29%

Abbreviations: BMI, body mass index; BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; HST, highly specialised technology; ICER, incremental cost effectiveness ratio; LEPR, leptin receptor; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Table 44: Exploratory analyses undertaken by the ERG (LEPR, adult)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from ERG corrected company base case
ERG corrected company base-case (LEPR, adult)		[redacted]	[redacted]	£183,648	-
Scenario 1: Modelled treatment effectiveness					
a) Alternative treatment efficacy assumption after trial duration (BMI regain)		[redacted]	[redacted]	£184,766	1%
b) Alternative treatment efficacy assumption after trial duration (BMI maintenance)		Not applicable for LEPR			
c) Treatment response rates based on BMI class		[redacted]	[redacted]	£181,769	-1%
d) Reduced setmelanotide efficacy during trial period (BMI drops by [redacted] for LEPR)		[redacted]	[redacted]	£191,237	4%
Scenario 2: 1% discontinuation rate per year throughout the lifetime horizon		[redacted]	[redacted]	£186,501	2%
Scenario 3: 3.5% discount rate for health outcomes		[redacted]	[redacted]	£291,474	59%

Scenario 4: Mortality					
a) No mortality benefit for responders		[redacted]	[redacted]	£248,630	35%
b) Non-responder and BSC life expectancy converted to equivalent HR multiplier		[redacted]	[redacted]	£186,657	2%
c) Company's base case mortality multiplier for non-responders and BSC decreased by 10%		[redacted]	[redacted]	£187,586	2%
d) Increased mean and maximum age life expectancy for non-responders and BSC (based on clinical opinion to ERG)		[redacted]	[redacted]	£208,431	13%
Scenario 5: Combined Hyperphagia scenario					
Alternative baseline distribution + transition probability (moderate to mild: 50% + disutility based on metreleptin appraisal (equivalent utility multiplier)		[redacted]	[redacted]	£215,508	17%
Scenario 6: 20-year time horizon		[redacted]	[redacted]	£239,644	30%
Scenario 7: Co-morbidity prevalence rates and disutility reduced					
a) Prevalence rates and disutilities decreased by 10%		[redacted]	[redacted]	£182,052	-1%
b) Paediatric patients assumed to have 10% lower prevalence rates and disutility compared to adults		[redacted]	[redacted]	£183,648	0%
Scenario 8: Setmelanotide dosing separately for paediatric and adults		[redacted]	[redacted]	£253,357	38%

Abbreviations: BMI, body mass index; BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; HST, highly specialised technology; ICER, incremental cost effectiveness ratio; LEPR, leptin receptor; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Table 45: Exploratory analyses undertaken by the ERG (POMC, paediatric)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from ERG corrected company base case
ERG corrected company base-case (POMC, paediatric)		[redacted]	[redacted]	£193,008	-
Scenario 1: Modelled treatment effectiveness					
a) Alternative treatment efficacy assumption after trial duration (BMI regain)		[redacted]	[redacted]	£245,590	27%
b) Alternative treatment efficacy assumption after trial duration (BMI maintenance)		[redacted]	[redacted]	£193,132	0%
c) Treatment response rates based on BMI class		[redacted]	[redacted]	£192,262	0%
d) Reduced setmelanotide efficacy during trial period (BMI drops by [redacted] for POMC)		[redacted]	[redacted]	£196,016	2%
Scenario 2: 1% discontinuation rate per year throughout the lifetime horizon		[redacted]	[redacted]	£201,449	4%
Scenario 3: 3.5% discount rate for health outcomes		[redacted]	[redacted]	£338,226	75%
Scenario 4: Mortality					
a) No mortality benefit for responders		[redacted]	[redacted]	£244,226	27%
b) Non-responder and BSC life expectancy converted to equivalent HR multiplier		[redacted]	[redacted]	£192,294	0%
c) Company's base case mortality multiplier for non-responders and BSC decreased by 10%		[redacted]	[redacted]	£194,249	1%
d) Increased mean and maximum age life expectancy for non-responders and BSC		[redacted]	[redacted]	£193,688	0%

(based on clinical opinion to ERG)					
Scenario 5: Combined Hyperphagia scenario					
Alternative baseline distribution + transition probability (Severe to mild: 33.3% + disutility based on metreleptin appraisal (equivalent utility multiplier)		[redacted]	[redacted]	£307,974	60%
Scenario 6: 20-year time horizon		[redacted]	[redacted]	£325,339	69%
Scenario 7: Co-morbidity prevalence rates and disutility reduced					
a) Prevalence rates and disutilities decreased by 10%		[redacted]	[redacted]	£194,902	1%
b) Paediatric patients assumed to have 10% lower prevalence rates and disutility compared to adults.		[redacted]	[redacted]	£193,091	0%
Scenario 8: Setmelanotide dosing separately for paediatric and adults		[redacted]	[redacted]	£160,076	-17%

Abbreviations: BMI, body mass index; BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; HST, highly specialised technology; ICER, incremental cost effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Table 46: Exploratory analyses undertaken by the ERG (POMC, adult)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from company base case
ERG corrected company base-case (POMC, adult)		[redacted]	[redacted]	£184,766	-
Scenario 1: Modelled treatment effectiveness					
a) Alternative treatment efficacy assumption after trial duration (BMI regain)		[redacted]	[redacted]	£237,134	28%
b) Alternative treatment efficacy assumption after trial duration (BMI maintenance)		[redacted]	[redacted]	£187,800	2%

c) Treatment response rates based on BMI class		[redacted]	[redacted]	£183,971	0%
d) Reduced setmelanotide efficacy during trial period (BMI drops by [redacted] for POMC)		[redacted]	[redacted]	£188,636	2%
Scenario 2: 1% discontinuation rate per year throughout the lifetime horizon		[redacted]	[redacted]	£187,661	2%
Scenario 3: 3.5% discount rate for health outcomes		[redacted]	[redacted]	£303,972	65%
Scenario 4: Mortality					
a) No mortality benefit for responders		[redacted]	[redacted]	£246,237	33%
b) Non-responder and BSC life expectancy converted to equivalent HR multiplier		[redacted]	[redacted]	£192,310	4%
c) Company's base case mortality multiplier for non-responders and BSC decreased by 10%		[redacted]	[redacted]	£194,167	5%
d) Increased mean and maximum age life expectancy for non-responders and BSC (based on clinical opinion to ERG)		[redacted]	[redacted]	£184,847	0%
Scenario 5: Combined Hyperphagia scenario					
Alternative baseline distribution + transition probability (Severe to mild: 33.3% + disutility based on metreleptin appraisal (equivalent utility multiplier)		[redacted]	[redacted]	£254,803	38%
Scenario 6: 20-year time horizon		[redacted]	[redacted]	£288,298	56%
Scenario 7: Co-morbidity prevalence rates and disutility reduced					
a) Prevalence rates and disutilities decreased by 10%		[redacted]	[redacted]	£186,157	1%

b) Paediatric patients assumed to have 10% lower prevalence rates and disutility compared to adults.		[redacted]	[redacted]	£184,766	0%
Scenario 8: Setmelanotide dosing separately for paediatric and adults		[redacted]	[redacted]	£179,070	-3%

Abbreviations: BMI, body mass index; BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; HST, highly specialised technology; ICER, incremental cost effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

6.3. ERG base case

The results based on ERG preferred base case assumptions have been outlined for each of the subpopulations in Table 47 to Table 50.

Table 47: Summary of ERG's preferred assumptions and ICER (LEPR, paediatric)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£165,424
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£166,843
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£215,295
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£233,466
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£230,521
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	£373,041

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; QALY, quality-adjusted life year

Table 48: Summary of ERG's preferred assumptions and ICER (LEPR, adult)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£181,769
ERG corrected company base case				

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£183,648
ERG's preferred base case				
Setmelanotide dose based on average adult dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£253,357
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£257,215
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£261,462
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	£407,126

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; QALY, quality-adjusted life year

Table 49: Summary of ERG's preferred assumptions and ICER (POMC, paediatric)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£191,348
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£193,008
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£160,076
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£166,888
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£164,045
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	£273,366

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

Table 50: Summary of ERG's preferred assumptions and ICER (POMC, adult)

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	*5.1.2*	[redacted]	[redacted]	£183,100
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	*6.1*	[redacted]	[redacted]	£184,766

Scenario	ERG report section	Incremental cost	Incremental QALYs	ICER
ERG's preferred base case				
Setmelanotide dose based on average adult dose from clinical studies	*4.2.6.6*	[redacted]	[redacted]	£179,070
1% discontinuation throughout lifetime	*4.2.6.2*	[redacted]	[redacted]	£181,835
Non-responder and BSC life expectancy converted to equivalent HR multiplier	*4.2.6.3*	[redacted]	[redacted]	£188,335
3.5% discount rate for health outcomes	*4.2.5*	[redacted]	[redacted]	£303,142

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life year

6.4. Conclusions of the cost-effectiveness section

Based on the ERG's preferred base case results, setmelanotide resulted in an ICER of £373,041; £407,126; £273,366 and £303,142 when compared to BSC in the LEPR paediatric, LEPR adult, POMC paediatric and POMC adult populations, respectively. The ERG's preferred assumption which had the most upward impact on the ICER was the use of a 3.5% discount rate for benefits. As mortality was fully modelled and based on assumption and clinical opinion, the ERG considered the NICE reference case discount of 3.5% to be more appropriate for decision-making. Overall, the ERG considered there to be a paucity of data with respect to key modelled inputs including mortality, long term treatment effectiveness and hyperphagia (particularly surrounding HRQoL values), which introduced uncertainty into the company's analysis.

7. SUBMISSIONS FROM STAKEHOLDERS

7.1. NHS England and NHS Improvement

A stakeholder submission was received from the NHS England (NHSE) and NHS Improvement, which provided comments on the current treatment of the condition, the potential use of setmelanotide and considerations relating to equality.

Consistent with the evidence presented by the company, the stakeholder indicated that there are no NHSE clinical commissioning policies for POMC or LEPR deficiency obesity. The submission by the stakeholder additionally indicated that, though there is no highly specialised service for these conditions, there is one centre of excellence and expertise in England; while the company indicated that all patients with this condition are currently managed at the University of Cambridge Metabolic Research Laboratories. The company anticipated that the decision to treat a patient with setmelanotide would be made at this centre, with referral to regional expert centres for monitoring, though the stakeholder highlighted uncertainty around the treatment pathway from local centres that is consistent with the understanding of the ERG. Furthermore, the stakeholder considered that the introduction of setmelanotide would have a large impact on the current pathway and indicated that it would work closely with the service to facilitate prescription, advice and monitoring.

The comments regarding the current use of setmelanotide in the local health economy and rules around treatment initiation were consistent with evidence presented by the company. The stakeholder further indicated that setmelanotide would be the first pharmacological treatment option for patients with POMC or LEPR deficiency obesity, and that it anticipated that the treatment would be administered through the national centre with no additional investments.

The stakeholder indicated that it is not aware of any evaluations or audits of the use of setmelanotide and had identified no potential equality issues to be considered.

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