NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from Rhythm Pharmaceuticals
   - Company submission
   - Company PAS submission

2. **Clarification questions and company responses**
   - Company response
   - Company response to further clarification

3. **Patient group, professional group and NHS organisation submission** from:
   - NHS England

4. **Expert personal perspectives** from:
   - Dr Mars Skae, clinical expert, nominated by Royal College of Paediatrics and Child Health
   - Dr Pooja Sachdev, clinical expert, nominated by Royal College of Paediatrics and Child Health
   - Professor Sadaf Farooqi, clinical expert, nominated by Rhythm Pharmaceuticals
   - Alexander Potter, patient expert, nominated by Professor Sadaf Farooqi
   - Debbie Potter, patient expert, nominated by Professor Sadaf Farooqi

5. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)

6. **Evidence Review Group report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Company submission of evidence for setmelanotide

July 2021

Contents

List of tables

List of figures

Glossary of terms

Term	Description
α-MSH	α-melanocyte-stimulating hormone
AE	Adverse event
AESI	Adverse event of special interest
AgRP	Agouti-related protein
AHI	Apnoea-hypopnea index
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BMI	Body mass index
BMI SDS	Body mass index standard deviation
BMI-Z	Body mass index z-score
BSC	Best supportive care
CCG	Clinical Commissioning Group
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CVD	Cardiovascular disease
DSM-III	Diagnostic and Statistical Manual of Mental Disorders
DUS	Designated use set
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment
EQ-5D	EuroQol five-dimension scale
EuroQoL	European Quality of Life Scale
FAS	Full analysis set
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP1	Glucagon-Like Peptide 1
GOOS	Genetics of obesity study
GP	General practitioner
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQL	Health-related quality of life
HST	Highly specialised technology
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ID	Identification number

Term	Description
IFU	Instructions for use
IR-HOMA	Homeostatic model assessment of insulin resistance
IRR	Incidence rate ratio
ISBN	International Standard Book Number
ITT	Intention-to-treat
IWQOL	Impact of Weight on Quality of Life
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
KOL	Key opinion leader
LDL	Low-density lipoprotein
LEP	Leptin
LEPR	Leptin receptor
LS	Least square
LYG	Life years gained
MAA	Marketing authorisation application
MC1	Melanocortin-1
MC3	Melanocortin-3
MC4R	Melanocortin-4 receptor
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MRU	Medical resource utilisation
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCT	National clinical trial
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
OWSA	One way sensitivity analysis
PCSK1	Proprotein convertase subtilisin/kexin type 1
PedsQL	Paediatric Quality of Life Inventory
PHQ-9	Patient Health Questionnaire-9
PICOS	Population, intervention, comparators, outcomes and study design
PIP	Personal independence payment
POMC	Proopiomelanocortin gene
PPL	Paediatric and primary lymphoedema
PRISM	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient reported outcome
Prof	Professor

Term	Description
PSS	Prescribed Specialised Services
PSSRU	Personal Social Services Research Unit
PWS	Prader-Willli syndrome
QALY	Quality-adjusted life year
QoL	Quality of life
RGDO	Rare genetic disorder of obesity
R-HOMA	Homeostatic model assessment
RR-P	Ratio of proportions
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SF-10	Short-form, 10 item
SF-36	Short-form, 36 item
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
SPC	Summary of product characteristics
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
US	United States
VAS	Visual analogue scale
WHO	World Health Organisation

Executive Summary

Please include a brief summary of the key points in the submission addressing:

- *Nature of the condition*
- *Impact of the new technology*
- *Cost to the NHS and Personal Social Services*
- *Value for money, including incremental QALYs and incremental cost per QALY as per company base case*
- *Impact of the technology beyond direct health benefits*

All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

The technology

Setmelanotide (IMCIVREE®) is a selective melanocortin-4 receptor agonist (Section 2.2) currently undergoing regulatory approval for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic proopiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Setmelanotide will be supplied as a 10 mg/ml solution for injection. Dosing is 1 mg – 3mg daily, depending on patient's age and response, and is administered by subcutaneous self-injection once daily in the morning. Patients who respond to an initial 12 weeks of treatment i.e. patients who lose at least 5 kg in body weight or ≥ 5% weight loss, are expected to continue treatment indefinitely.

Nature of the condition

POMC/PCSK1 and LEPR deficiencies are rare genetic disorders of obesity (RGDOs) most appropriately described as hypothalamic disorders affecting the MC4R neuroendocrine system responsible for regulating hunger, satiety and energy expenditure. Both deficiencies are characteristed by severe obesity with onset in infancy accompanied by hyperphagia: an overwhelming, heightened and relentless hunger mimicking feelings of starvation, longer time to reach satiety and shorter duration of satiety and severe preoccupation with food leading to persistent and extreme food seeking behaviour (Section 6.1.) Currently there are no treatments that specifically target the underlying disease; diet and exercise are often recommended but attempts to control food intake are hampered by hyperphagia and patients continue to gain weight throughout their lifetime. Other treatments such as orlistat, methylcellulose and bariatric surgery are equally ineffective in these patient populations and their use is not recommended. Patients who have undergone bariatric surgery have been reported to regain weight due to persisting hyperphagia.

Many patients suffer from mobility and joint problems as well as deformities of the legs as a result of carrying excess weight on a developing skeleton. Other common comorbidities are non-alcoholic fatty liver disease (NAFLD), sleep apnoea, type 2 diabetes and respiratory infections and disorders such as asthma. Patients' normal social development can also be affected as socialising and participating in education can become difficult with repercussions for mental health as well (Section 7.1). Parents/carers of children with POMC/PCSK1 and LEPR deficiency obesity report the challenging nature of caring for a child with hyperphagia and the psychological difficulties of attempting to unsuccessfully regulate food intake. Coupled with the social stigma of having an obese child, the distress for parents can be considerable (Section 7.1).

Impact of the new technology

The safety and efficacy of setmelanotide was investigated in two pivotal phase 3 trials, the first, RM-493-012 included POMC/PCSK1 patients whilst the second, RM-493-015 included LEPR patients. Both trials were otherwise identical in design in that they were non-randomised, single-arm, open-label studies including a double-blind placebo-controlled withdrawal period. Adult patients in each of the trials received a setmelanotide starting dose of 1 mg per day that was up-titrated to achieve an individualised therapeutic dose; paediatric patients received a starting dose of 0.5 mg per day and was similarly up-titrated. Participants who reached the target weight loss threshold by Week 12 of treatment entered a double-blind, placebo-controlled withdrawal period, to receive setmelanotide or placebo-control for 4 weeks. After completion of the withdrawal phase, patients returned to the previously established setmelanotide dose for a further 32 weeks. Over the entire 52-week study period, patients received active setmelanotide treatment for a total of 48 weeks. The primary endpoint was the proportion of patients with 10% reduction in weight from baseline (Section 9.4.1). A long-term extension study (RM-493-022) of up to 2 years in patients who had completed a previous study with setmelanotide also provides data for this submission.

Results from the two pivotal phase 3 trials showed (Section 9.6.1):

- In total, 85.7% (12/14, 90% CI [61.46; 97.40]) of POMC/PCSK1 patients and 53.3% (8/15, 90% CI [30.00; 75.63]) of LEPR patients in the combined cohorts showed at least a 10% weight loss at 52 weeks from inclusion ($p < 0.0001$).

- A mean decrease in the highest hunger score of 42.7% ($p<0.0001$) for the 10 LEPR patients in the combined cohorts and 27.1% for the 7 POMC/PCSK1 patients (5.8 vs 8.1 $p=0.0005$) in the pivotal cohort of the designated use population (DUS) aged 12 years and older.

- A mean decrease of [redacted]% in the mean BMI of POMC/PCSK1 patients from severe obesity (mean BMI at inclusion of [redacted] kg/m2) to overweight (mean BMI of [redacted] kg/m2 at one year of treatment, $p < 0.0001$);

- A mean decrease of [redacted]% in the mean BMI of LEPR patients from massive obesity (mean BMI at inclusion of [redacted] kg/m2) to severe obesity (mean BMI of [redacted] kg/m2 at one year of treatment, p<0.0001).

The main adverse events reported during the trials included injection-site reactions, changes in skin pigmentation and nausea.

During a qualitative study conducted in Germany, trial participants described the benefits of setmelanotide treatment on their lives including the impact on their psychological and physical functioning, number of hospital admissions, their ability to work, their relationships and educational attainment (Section 7.2).

Value for money

A model was developed to estimate the cost-effectiveness of setmelanotide treatment compared with best supportive care (diet and exercise advice). The model employs a cohort-based Markov (state-transition) approach with multiple health states stratified by the BMI/BMI-Z score for both adult and paediatric populations, as well as a death state. Furthermore, the model tracks medical resource utilisation (MRU) costs for the treatment of obesity, accounts for the utility associated with hyperphagia, and accrues the costs and disutilities associated with the most relevant obesity-related complications in this patient population (including sleep apnoea, osteoarthritis, non-alcoholic fatty liver disease [NAFLD], type 2 diabetes mellitus [T2DM], and cardiovascular disease [CVD]). Eligible patients in the model are treated with either BSC or a combination of setmelanotide and BSC. Markov health states in the model are BMI/BMI-Z and death. Treatments can affect both BMI/BMI-Z (inducing either weight loss, maintenance, or regain), and hyperphagia, which is not modelled as separate set of health states but treated as a condition within each BMI/BMI-Z health state and assigned a separate utility corresponding to severity (mild, moderate, or severe). Changes in BMI over time in the model lead to changes in obesity-related comorbidities, which are also tracked as conditions within each BMI health state, and incur both treatment costs and a disutility, and increased risk of mortality. Patients from

any BMI health state can move to the death state as a consequence of complications from comorbidities of obesity in addition to other common conditions such as infections and immunodeficiency (Section 12.1.3).

In the base-case Setmelanotide + BSC accrued [redacted] incremental QALYs and £2,620,816 incremental costs over a lifetime time horizon. This corresponds to an ICER of £176,913 per additional QALY gained over BSC alone (Section 12.5.1). the estimated budget impact in year 1 is [redacted] rising to [redacted] in year 5 (Section 13.7).

A patient access scheme offering a [redacted]% discount on the NHS list price of [redacted] per patient per year is proposed resulting in incremental costs of [redacted] over a lifetime time horizon and an ICER of £141,550 per additional QALY gained over BSC along (PAS evidence submission).

Impact of the technology beyond direct health benefits

The introduction of setmelanotide is a step change in the treatment of POMC/PCSK1 and LEPR deficiencies, providing an effective treatment option for a group of patients for whom there is currently nothing. POMC and LEPR deficiencies have a significant impact on the lives of both the patients and their parents/caregivers. With onset of obesity in infancy and weight gain continuing through childhood and adolescence, a period of time crucial for social development, these patients can be severely affected by bullying, reduced self-esteem and poorer educational attainment (Section 14.1), on top of the well known health detriments of severe obesity. Hyperphagia can constrain patients' lives further with constant food seeking behaviour interfering with the ability to work, study and socialize. Parents/caregivers are also affected by this behaviour with their inability to control the amount food their child is eating, whilst their child continues to gain weight being a major source of distress. The stigma of having an obese child can also affect caregivers' mental health.

It is anticipated that setmelanotide treatment will be initiated at a national expert centre and that all treatment decisions would be made by the national

expert with patients referred back to local centres for maintenance treatment. Patients will receive setmelanotide via Home delivery for self-administration. The introduction of setmelanotide will thus support the NHS in providing an effective service for a group of patients for whom there is currently no effective treatment.

Section A - Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1 Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
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.		
Intervention	Setmelanotide	Setmelanotide in combination with standard management	Setmelanotide is not expected to replace standard management in treatment obesity patients with genetic POMC/PCSK1 or LEPR deficiencies, rather it is expected to improve the impact

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
			of those interventions after an initial weight-loss period following treatment with setmelanotide
Comparator(s)	• standard management without setmelanotide (including a reduced calorie diet and increased physical activity) • orlistat • methylcellulose • bariatric surgery	Only standard management without setmelanotide have 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 in not maintained (1). In addition, KOL opinion is that it is potentially harmful to reduce stomach size in a patient with untreated hyperphagia
Outcomes	The outcome measures to be considered include: • BMI • BMI-Z • weight loss • percentage body fat • waist circumference • hunger • incidence of type 2 diabetes • cardiovascular events • mortality • co-morbidities associated with early	Outcomes include: • BMI • BMI-Z • Weight loss • Hyperphagia • Obstructive sleep apnoea • Osteoarthritis • NAFLD • Type 2 diabetes • CV events • Mortality • HRQL (patients)	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

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	onset severe obesity including cancer • adverse effects of treatment • health-related quality of life (for patients and carers).		to setmelanotide treatment 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.
Subgroups to be considered			
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options		
Cost to the NHS and PSS, and Value for Money	• 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 o Incorporation of genetic testing as part of clinical practice		

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.		
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements		

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: IMCIVREE®

UK Approved name: Setmelanotide

Therapeutic class: Melanocortin-4 receptor (MC4R) agonist

2.2 What is the principal mechanism of action of the technology?

Setmelanotide is a selective MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4

receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4 receptor as a result of genetic defects, including POMC and LEPR deficiency, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure (Figure 1). Nonclinical evidence shows that MC4 receptors are important for setmelanotide-regulated appetite and weight loss. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light (2).

Figure 1 Schematic illustration of setmelantoide's mechanism of action on the MC4R pathway

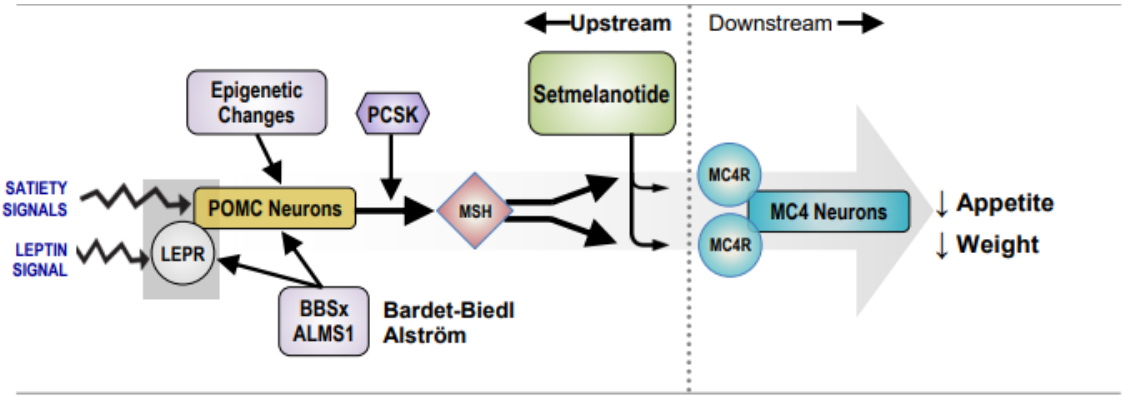


Table 2 Dosing information of the technology being evaluated

Pharmaceutical formulation	Subcutaneous injection
Method of administration	Setmelanotide should be injected subcutaneously in the abdomen, thigh, or arm, rotating to a different site each day. If a dose is missed, the once daily regimen should be resumed as prescribed with the next scheduled dose. IMCIVREE must not be administered intravenously or intramuscularly.
Doses	**Adult population:** 2 mg once daily subcutaneous injection for 2 weeks. Then, if well tolerated dose can be increased to 3 mg once daily Paediatric population: • Patients aged 6 to 17 years - 1 mg once daily subcutaneous injection for 2 weeks If tolerated after 2 weeks, the dose can be increased to 2 mg once daily • Patients aged 12 to 17 – If weight remains above the 90th percentile with the 2 mg once daily subcutaneous injection and additional weight loss is desired, the dose may be increased to 3 mg once daily

	If dose escalation is not tolerated, paediatric patients may maintain administration of the 1 mg once daily dose
Dosing frequency	Setmelanotide should be injected once daily, at the beginning of the day (to maximise hunger reduction during awake period), without regard to the timing of meals.
Average length of a course of treatment	Setmelanotide is a life-long treatment
Anticipated average interval between courses of treatments	n/a
Anticipated number of repeat courses of treatments	n/a
Dose adjustments	No dose adjustments are required in patients with mild renal impairment. For patients with moderate renal impairment, it is recommended that the dose be titrated. If the 2 mg once daily dose is well tolerated and additional weight loss is desired, the dose can be increased to 3 mg once daily. It is not recommended to administer IMCIVREE to patients with severe renal impairment.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Positive CHMP opinion was received on 20 May 2021 and final MAA is expected 26 July 2021.

Following CHMP positive opinion, an application for a Great Britain Marketing Authorisation for IMCIVREE was submitted under the European Commission Decision Reliance Procedure to the MHRA on 31 May 2021, with approval expected for end of July 2021 within a few days of EMA formal approval.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Setmelanotide is expected to be available in the UK in the second quarter of 2022.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Setmelanotide is currently approved by the FDA for chronic weight management in adult and paediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing.

3.4 If the technology has been launched in the UK provide information on the use in England.

Setmelanotide has not been launched in the UK yet.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Study RM-493-014 is a Phase 2, open-label, non-randomised, basket study to evaluate the effects of setmelanotide on body weight change, hunger score and other factors. This study includes patients with various genetic deficiencies (POMC, PCSK1, LEPR, Bardet-Biedl syndrome, Alström syndrome, Smith-Magenis syndrome, Carboxypeptidase E syndrome, SH2B1 haploinsufficiency, leptin-deficiency obesity). The primary end point is achieving 5% weight reduction vs. baseline at 3 months. Fifty-two week efficacy data are also being collected. One patient included in the trial meets the inclusion criteria for this submission. The estimated completion date is in December 2021.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

The NICE HST assessment is currently the only evaluation the technology has been planned to undergo within the UK. The manufacturer has not planned to make a submission to SMC as there are [redacted] documented cases of obesity associated with LEPR or POMC deficiency in Scotland.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

It is not anticipated that this evaluation would exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

5.2 How will the submission address these issues and any equality issues raised in the scope?

N/A

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Although human obesity is recognised as being influenced by both genetic and environmental factors, extreme morbid obesity with an onset in infancy or early childhood is often found to be more clearly caused by specific genetic contributors. The identification of key genetic determinates of the neuronal pathways and signalling molecules regulating appetite and body weight has led to the discovery of multiple rare genetic disorders of obesity (3).

Rare genetic disorders of obesity (RGDOs) are poorly diagnosed, and often characterised by severe obesity or obesity Class III (classified by the NHS as a BMI ≥ 40.0 kg/m^2, in children at BMI ≥99th percentile) (4-6). Proopiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity are two such RGDOs. Patients with POMC and LEPR gene mutations exhibit a clinical onset very early in life, often beginning in infancy, with a voracious, overactive appetite and pronounced hyperphagic feeding behaviours leading to rapid weight gain that is associated with obesity. Remarkable weight increases over many standard deviations (SDs) from the normal weight growth curves are typical in these patients (7). According to Prof Farooqi's expert opinion, as patients grow and develop, paediatric weight curves demonstrate progressive and severe weight gain, often tracking >3 SDs above normal weights for age and leading ultimately to adult body mass index (BMI) values >40 kg/m^2. Consequently, patients often suffer from mobility and joint problems as well as deformities of the legs due to carrying excess weight on a developing skeleton (8). Other common comorbidities are non-alcoholic fatty liver disease (NAFLD), sleep apnoea, type 2 diabetes and respiratory infections and disorders such as asthma due to impaired lung development. The combination of obesity and respiratory infections is a leading cause of premature death in particularly in LEPR patients (8).

In contrast to general obesity, these genetic forms of obesity are most appropriately described as hypothalamic disorders affecting the MC4R neuroendocrine system responsible for regulating appetite and food intake resulting in hyperphagia. Hyperphagia is characterised by an overwhelming, heightened, and relentless hunger mimicking feelings of starvation; longer time to reach satiety and shorter duration of satiety; severe preoccupation with food; persistent and potentially extreme food-seeking behaviours (such as night eating, stealing food, and eating non-food items); and distress or inappropriate behavioural response if denied food (9). Consequently, this behaviour leads to excess energy intake (10), and patients continue to gain weight throughout their lifetime (11). Hyperphagia also has a negative impact on quality of life, with patients reporting being so preoccupied with food and the desire to eat that it dominates their life, affecting concentration, productivity and education (data on file).

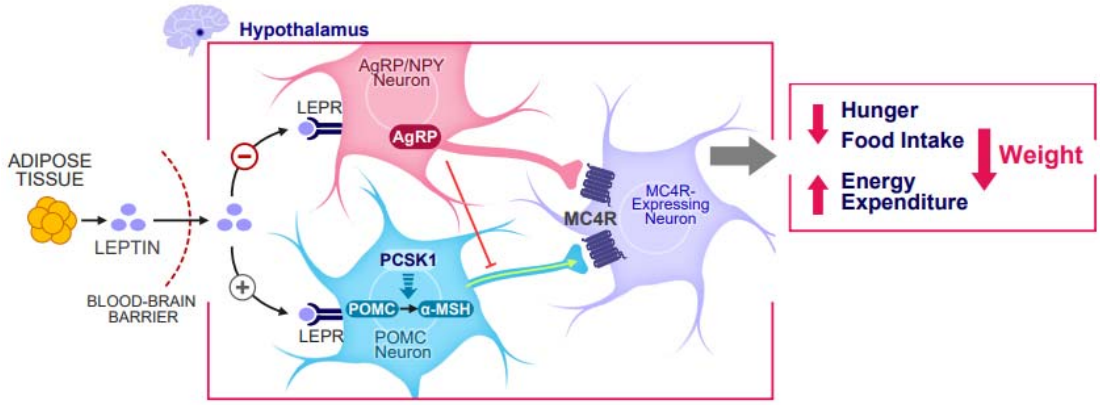
The MC4R pathway

The melanocortin 4 receptor (MC4R) pathway in the hypothalamus regulates homeostatic functions including appetite, caloric intake and energy expenditure. Its purpose is to defend against starvation by promoting hunger and food seeking behaviour (12). Activation of MC4R suppresses food intake; inhibition of MC4R causes increased food intake (13). Activation and inhibition of MC4R is controlled by two distinct populations of neurons which lie directly upstream of the receptor; One releases POMC-derived melanocortin peptides (with the primary function of suppressing appetite); the other releases Agouti-related protein (AgRP, primary function to stimulate appetite).

In healthy individuals, in the fasted state, low levels of leptin stimulate AgRP neurons and inhibit POMC neurons, resulting in more antagonism of the MC4R than agonism, thereby reducing the MC4R signal and increasing food intake. Conversely, in the fed state (Figure 2), higher levels of leptin stimulate POMC neurons and inhibit AgRP, resulting in more agonism of the MC4R than antagonism, thereby reducing food intake. It should be noted that these are not on/off signals and that the relative amount of POMC or AgRP released

determines the degree of activation of MC4R, or melanocortin tone, thereby modulating food intake.

Figure 2 Schematic outlining healthy signalling in MC4R pathway in the fed state



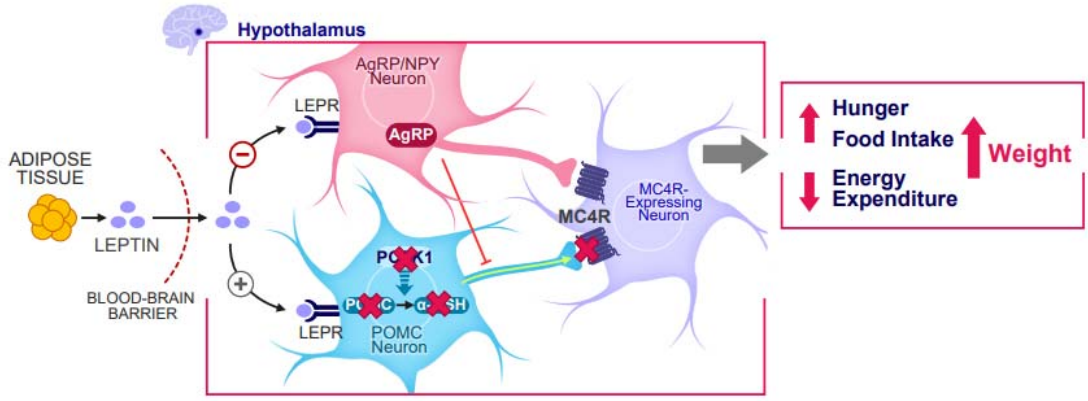
POMC/PCSK1 deficiency obesity

In this disease, neuropeptides, such as α-melanocyte-stimulating hormone (α-MSH), which are synthesised and processed from the POMC gene are absent or deficient due to defects that may occur in one of two genes. Specifically, POMC deficiency results from one of two different homozygous genetic defects, both upstream of MC4R: 1) loss of function mutations in the POMC gene itself or 2) mutations in the Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) gene, which encodes the proprotein convertase subtilisin/kexin type 1 that processes POMC into derivative MSH neuropeptides that bind to MC4R in target hypothalamic neurons (3, 14-16). Therefore, POMC deficiency obesity is caused by two monogenic disorders resulting in missing MSH neuropeptide synthesis and/or processing, with subsequent absence of signalling through the MC4 pathway. This manifests as hyperphagia and lack of satiety, thereby driving severe obesity. Patients with POMC deficiency obesity often weigh over 100 kg by age 6 to 8 years (17).

POMC deficiency is often accompanied by adrenocorticotrophic hormone deficiency and individuals may also have mild central hypothyroidism, red hair and pale skin (4, 10). Individuals who are homozygous or compound heterozygous for variants in PCSK1 are similarly associated with experiencing severe obesity beginning early in life and may also be accompanied by small

bowel enteropathy, adrenocorticotrophic hormone deficiency, hypothyroidism, hypoglycaemia, and diabetes insipidus (4, 18, 19).

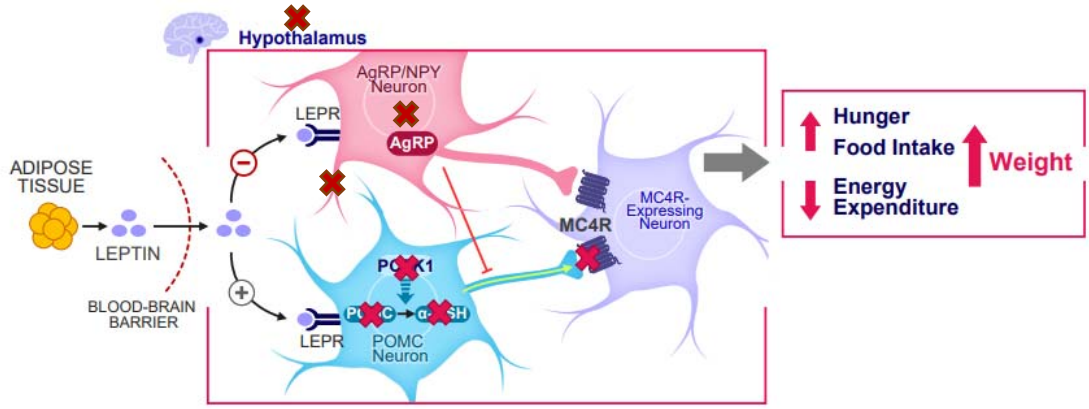
Figure 3 Schematic outlining interruption to signalling in MC4R pathway due to POMC/PCSK1 deficiency



LEPR deficiency obesity

In LEPR deficiency, the mutation affects the LEP receptor, which is expressed on both POMC and AgRP neurons. Consequently, patients with LEPR deficiency cannot regulate POMC or AgRP neurons. In addition, LEPR is expressed on other (non-melanocortin) neuronal populations both within the hypothalamus and in other areas involved in food reward such as the striatum and ventral tegmental area. As such, the hyperphagia and obesity in LEPR deficient patients is usually more severe than that seen in POMC deficiency. In addition to hyperphagia and severe obesity, LEPR deficiency may be accompanied by hypothyroidism, hypogonadotropic hypogonadism, metabolic dysfunction, immune dysfunction (i.e., frequent infections), and growth hormone deficiency leading to reduced adult height (4, 10). Some patients do not experience pubertal development which may lead to reduced height in adulthood, but spontaneous pubertal development has also been noted in cases of LEPR deficiency (4, 18).

Figure 4 Schematic outlining interruption to signalling in MC4R pathway due to LEPR deficiency



Diagnosis

RDGOs can be difficult to diagnose and in the first instance, patients with obesity associated with LEPR and POMC deficiency generally receive diet and lifestyle advice, which given the nature of the disease, specifically, patients' intense hypothalamic drive to eat, are ultimately unsuccessful. Currently, genetic testing would only take place following these unsuccessful attempts to control weight with diet and exercise, which slows down diagnosis and results in significant distress to both the patient and their parent/caregiver, who may believe that they are to blame for their inability to lose weight or, in the case of the parent, their inability to control their child's eating. Genetic testing for RGDOs has recently been adopted by the NHS, and it is hoped that earlier testing of children who present with early onset extreme obesity will help to reduce the psychological burden of obesity in these patients and enable commencement of appropriate treatment to correct the faulty MC4R pathway and the resultant health issues.

Prognosis

There are scarce data on mortality, but clinical opinion is that life expectancy of both LEPR and POMC/PCSK1 deficiency patients is significantly reduced, primarily due to accruing complications of obesity from such a young age. Prof. Farooqi's expert opinion reveals that LEPR deficiency is associated with a particularly high severity in terms of obesity, and this coupled with LEPR

patients' slightly compromised immune function contributes to a significant mortality rate from respiratory infections, often in childhood (8). Some of these cases are reported in the literature (20).

Data from general obesity can provide some insights into the range of comorbidities that might be experienced by LEPR and POMC/PCSK1 patients, however, the conditions are not comparable; LEPR and POMC/PCSK1 deficiencies having been described as an accelerated form of severe obesity (Prof Farooqi). Extrapolating data from the general obesity population to patients with genetic obesity due to LEPR or POMC/PCSK1 deficiency can therefore be considered a very conservative approach.

Overweight and obese men and women, are generally at an increased risk of a range of comorbidities including malignancies, cardiovascular disorders, and other chronic conditions compared to their counterparts of normal weight (21). A systematic literature review and meta-analysis reported the relative risk of such comorbidities in studies evaluating overweight and obese adults compared with those with normal BMI. For obese patients compared with individuals of normal BMI, there was a statistically significantly increased risk of all evaluated comorbid diseases except oesophageal cancer and prostate cancer (21). Incidence risk ratios (for comorbidities with available person-time data) and ratios of proportions (for comorbidities without available person-time data) are reported in **Error! Reference source not found.**. Obesity in children has also been associated with obstructive sleep apnoea, impaired lung development, musculoskeletal problems and non-alcoholic fatty liver disease (22, 23).

Table 3 Relative risk of comorbidities in adults with general obesity vs normal weight by BMI

Comorbidity	Pooled IRR	95% CI
Type II Diabetes[a]		
Men	6.74	5.55, 8.19
Women	12.41	9.03, 17.06
Obstructive sleep apnoea	NR	NR
Dyslipidaemia	NR	NR
Hypertension		
Men	1.84	1.51, 2.24

Comorbidity	Pooled IRR	95% CI
Women	2.42	1.59, 3.67
Breast Cancer	1.13	1.05, 1.22
Endometrial Cancer	3.22	2.91, 3.56
Ovarian Cancer	1.28	1.20, 1.36
Colorectal Cancer		
Men	1.95	1.59, 2.39
Women	1.66	1.52, 1.81
Esophageal Cancer		
Men	1.21[b]	0.97, 1.52
Women	1.20[b]	0.95, 1.53
Kidney Cancer		
Men	1.82	1.61, 2.05
Women	2.64	2.39, 2.90
Pancreatic Cancer		
Men	2.29	1.65, 3.19
Women	1.60	1.17, 2.20
Prostate Cancer	1.05	0.85, 1.30
Stroke		
Men	1.51[c]	1.33, 1.72
Women	1.49[c]	1.27, 1.74
Coronary Artery Disease		
Men	1.72	1.51, 1.96
Women	3.10	2.81, 3.43
Congestive Heart Failure		
Men	1.79	1.24, 2.59
Women	1.78[c]	1.07, 2.95
Asthma		
Men	1.43[c]	1.14, 1.79
Women	1.78[c]	1.36, 2.32
Chronic Back Pain		
Men	2.81[c]	2.27, 3.48
Women	2.81[c]	2.27, 3.48
Osteoarthritis		
Men	4.20	2.76, 6.41
Women	1.96	1.88, 2.04
Pulmonary Embolism		
Men	3.51	2.61, 4.73
Women	3.51	2.61, 4.73

Comorbidity	Pooled IRR	95% CI
Gallbladder disease		
Men	1.43[d]	1.04, 1.96
Women	2.32[d]	1.17, 4.57

BMI = body mass index; CI = confidence interval; IRR = incidence rate ratio; NR = not reported; RR-P = ratio of proportions

[a] Calculated across all BMI categories

[b] Data from one study reported risk ratio instead of pooled IRR

[c] RR-P reported instead of IRR where person-time data unavailable

[d] Pooled IRR and RR-P estimates for calculation of relative risk

Source: Guh et al., 2009.(21)

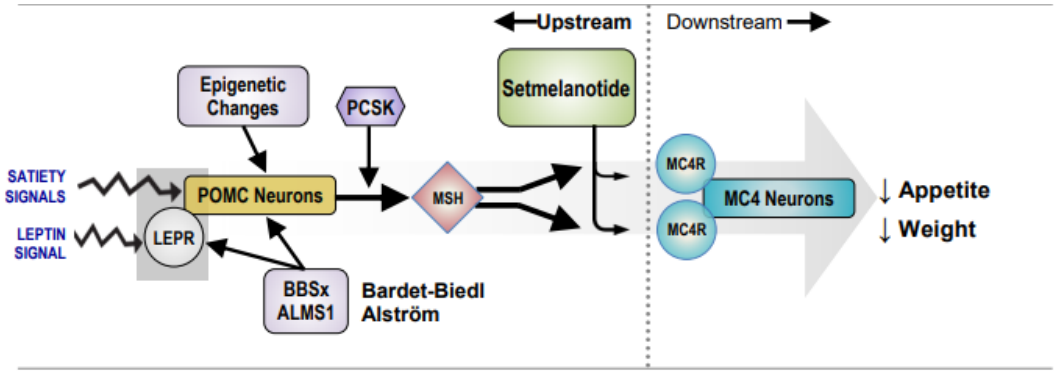
Depression and anxiety

Patients with extreme BMI also suffer from depression, anxiety, self-isolation, missed school days, and academic or professional underachievement (24, 25). The literature suggests there is a strong correlation between obesity and some psychiatric disorders, including depression and attention deficit hyperactivity (24). There is evidence that obesity is associated with one or more episodes of depression, which may be explained by structural changes in the brain that occur among obese and recurrently depressed people, particularly in the hippocampus where emotions are regulated. Stable factors like obesity could also contribute to the development of recurrent depression (26).

Setmelanotide

Setmelanotide is an MC4R agonist that will be the first treatment to target the neuronal pathways involved in obesity caused by POMC/PCSK1 or LEPR deficiency. By directly restoring lost agonist activity at the MC4R, upstream defects in the POMC neurons or to LEPR on POMC neurons can be bypassed (27). For patients with POMC/PCSK1 deficiency setmelanotide thus may serve as a replacement therapy to re-establish weight and appetite control in patients with these RGDOs. As described in Section **Error! Reference source not found.**LEPR deficiency is mediated by both melanocortin (Setmelanotide-responsive) and melanocortin-independent (Setmelanotide-unresponsive) pathways. Thus, setmelanotide corrects the melanocortin-dependent pathways with a positive impact on weight and appetite.

Figure 5 Graphical illustration of setmelanotide's mechanism of action on the MC4R pathway



6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

Approximately 88 cases of LEPR deficiency have been reported worldwide in the medical literature, 21 of which are European (28). LEPR deficiency affects approximately 2–3% of people with severe early-onset obesity (17) and is known to affect approximately 0.1 in 10,000 people in the European Union (29).

Approximately 50 cases of POMC deficiency have been reported in the medical literature (17) and it is known to affect less than 0.1 in 10,000 people in the European Union (30).

It is currently very difficult to estimate the exact number of patients with obesity associated with LEPR or POMC deficiency but given the rarity of these RGDOs globally, the number of patients in the UK is anticipated to be very low. Currently, there are around [redacted] patients who have been identified and diagnosed with genetic obesity due to LEPR, POMC/PCSK1 deficiency in the UK. It [redacted] anticipated that this number is likely to rise significantly following the introduction of setmelanotide and wider rollout of genetic testing within the NHS. The manufacturer anticipates that the number of patients who will meet the eligibility criteria for setmelanotide may go up to [redacted] patients in the UK in the next five years. Of note, setmelanotide is indicated only for those patients with biallelic LEPR or POMC deficiency confirmed by genetic analysis of variants.

6.3 **Please provide information about the life expectancy of people with the disease in England and provide the source of data.**

There is no published data on life expectancy or all-cause mortality for patients with genetic obesity due to LEPR or POMC deficiency. Expert opinion suggests that these conditions can be fatal to patients and that currently a significant proportion of LEPR patients die early in their childhood, typically by the age of 10 years due to the absence of any treatment options.

The association between high BMI and mortality has been documented, with a reduction in life expectancy at age 40 of 9.1 years for men and 7.7 years for women with class III obesity (30). Whilst these data demonstrate the significant impact of general obesity on life expectancy, expert opinion is that they significantly underestimate the impact of obesity due to LEPR or POMC deficiency on mortality. A leading expert into the deficiencies estimates there are less than 10 LEPR and POMC combined, middle aged patients worldwide.

7 Impact of the disease on quality of life

7.1 **Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).**

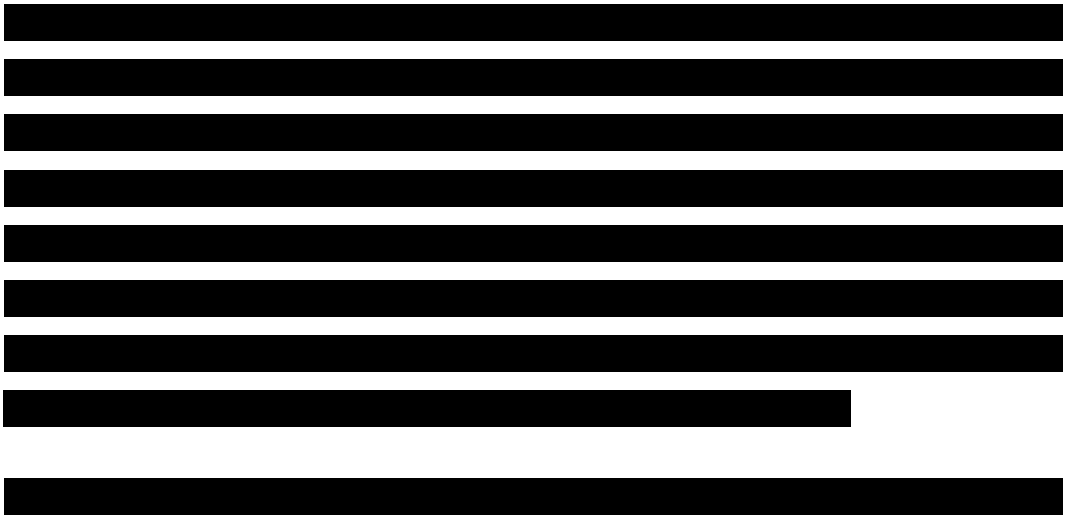
There have not been any studies specifically addressing the QoL of patients with POMC or LEPR deficiency. Two key elements affecting QoL in these patients are obesity itself and hyperphagia, which can impact patients' ability to participate in normal life due to the preoccupation with food. Literature on general childhood obesity suggests there are several well-documented adverse consequences, including hypertension, left ventricular abnormalities, insulin resistance, type 2 diabetes, NAFLD and obstructive sleep apnoea. LEPR and POMC/PCSK1 patients can also suffer from broader lung disfuction such as asthma and frequent lung infections. Additional complications of obesity include menstrual problems, polycystic ovarian disease, orthopaedic issues and psychological stress, which all result in poor quality of life in these patients (22).

Depression and social isolation

Obesity and RGDO linked to MC4R gene variants are also associated with the development of depression and social isolation in children and adolescents (24) and general obesity carries a clear social stigma across societies (31). Consistent with these findings, adults with obesity (BMI ≥30 kg/m2) have been found to be at an increased risk of the onset of major depressive disorder (26) and some other mental disorders, including increased risk of low self-esteem, mood disorders, motivational disorders, eating problems, impaired body image and interpersonal communication issues, which all affect patients' quality of life (32).

Childhood obesity leads to truancy, poorer performance at school, and more difficulty in completing higher education. Obese children are less successful and more often victims of school bullying (3 times more than other children). Adults are less likely to have a job, and when they do work, they are more absent and less productive (33).

A qualitative research study was set out where participants in the RM-493-022 study were interviewed to explore the experience of these conditions among patients with POMC and LEPR deficiency (34). Several patients reported experiences of social isolation while they were attending high school.



Obese people are victims of numerous discriminations that affect all dimensions of life (35). An obese person may be criticised or judged negatively by civil society and the health care community. They are often held responsible for their situation and for the failure of the treatment. Negative messages can increase a feeling of guilt that is often present (36).

[redacted]

Excess weight leads to morphological and aesthetic consequences (stretch marks, gynecomastia, hypersudation, buried penis, etc.) which can be a source of physical and psychological suffering, particularly for children and adolescents (37).

[redacted]

Impaired sexual life

There is evidence suggesting that obesity is associated with an increased risk of poorer sexual health in both men and women, including lack of enjoyment of sexual activity, lack of sexual desire, difficulties with sexual performance, and avoidance of sexual encounters. Higher BMI was found to be correlated with greater impairments in sexual quality of life, especially in obese women and individuals with class III obesity (38).

Reduced QoL due to hyperphagia

In addition to the negative impact on HRQL of obesity itself, patients with obesity due to POMC and LEPR deficiency have to deal with the negative effect of hyperphagia, which can be so severe as to dominate a patient's life. Data from studies on hyperphagia in patients with Prader-Willi syndrome (PWS) indicate that consistent hyperphagia presents an overwhelming burden on both patients who experience it, as well as their families and caregivers (9).

A study evaluated the burden of illness and effect on QoL of hyperphagia and severe obesity in patients with genetic obesity disorders or clinical diagnoses of severe obesity in Europe (Germany, France, UK, Italy, and Spain). Forty percent of the patients evaluated self-reported hyperphagia. Of adults (n=56) and children (n=4; based on caregiver questionnaires) evaluated, 32% reported severe to extremely severe pain or discomfort, 32% reported severe to extremely severe anxiety or depression, and 18% reported severe problems doing usual activities. Greater than 40% of evaluated patients reported feelings of hopelessness (46%), disliking themselves (44%), and painful or stiff joints (65%). Patients also reported numerically lower mean index (0.60) and visual analogue scale (VAS; 49.5) scores in the EuroQol 5-domain scale compared to the average for the evaluated European countries (index: 0.89; VAS: 77.8) (33).

Impact on parents and caregivers

The effects of obesity associated with LEPR and POMC deficiency are also felt by parents and caregivers, negatively impacting their HRQL. In some cases, children's cravings for food are so overwhelming that parents have no other choice but lock the fridge and cupboards or hide all food items in their homes.

Experts reveal that parents describe this denial of food to their children as "psychologically difficult". Moreover, their children become so heavy from very early on in their life that their parents are unable to lift them, which might be perceived as neglecting the child. Also, parents cannot take part in standard play activities with their children due to their reduced mobility. In addition to

this, the stigma of having an obese child can cause significant distress and parents may blame themselves for not being able to control what their child eats. In some cases, social services have become involved in the belief that the child's obesity is due to a lack of care from the parents, creating a very distressing situation for all involved. Relationships between parents and children can also become strained as parents are forced to act as the gatekeepers of food.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Setmelanotide has the potential to significantly impact both the quality and quantity of life of patients with POMC or LEPR deficiency. By correcting the underlying causes of these RGDOs and preventing its occurrence in early childhood it would be biologically plausible that patients treated with setmelanotide from infancy will be at a reduced risk of accumulated complications associated with early onset obesity (39), (40) and therefore life expectancy should not differ significantly from that of the general population. This is in contrast to high early mortality rates seen in untreated disease.

Patients who have received setmelanotide have described the impact it has had on their lives, ranging from the impact on their psychological and physical functioning, number of hospital admissions, their ability to work, their relationships and educational attainment. The following findings are taken from the Rhythm PPL patient interviews report, a qualitative study conducted in Germany to explore the experience of patients treated with setmelanotide (34).

All participants reported significant changes in their hunger following treatment with setmelanotide, including their ability to cope with feelings of hunger and choosing to eat healthier foods when they are hungry.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Participants also noted their improved general health and that this impacted on their ability to work and study:

[redacted]

[redacted]

Participants also reported that their weight loss had had a big impact on their mother:

[redacted]

Participants unequivocally indicated that the improvements seen in their hunger were very meaningful to them:

[redacted]

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are currently no existing guidelines for managing RGDOs caused by LEPR or POMC deficiency. In the UK, best supportive care (BSC) for patients with obesity associated with LEPR or POMC deficiency defaults to general obesity care. Existing guidelines focus on the management of general obesity.

It should be noted that many of the recommendations for treating general obesity are not effective or not appropriate for patients with LEPR or POMC deficiency obesity as they do not restore the impairment of the MC4R pathway experienced by this patient population (41-44).

- NICE clinical guideline 189 ‘Obesity: identification, assessment and management Preventing excess weight gain (2015) (6)
- NICE guideline NG7. Preventing excess weight gain (2015) (45)
- NICE guideline CG43. Obesity prevention (2006) (46)

The NHS clinical pathway for adults with general obesity is stratified into a tier-based service system. Tier 1 obesity services within NHS include campaigns, which promote reinforcement of healthy eating and physical activity guidelines. Tier 1 is delivered by local and regional public health teams, together with the identification and advice, often carried out in a primary care setting. Tier 2 obesity services typically comprise community-based or GP-led lifestyle weight management, which provides diet, nutrition, lifestyle and behaviour change advice, normally in a group setting environment. To use Tier 3 services, patients need to be referred to specialist weight management services, which are clinician-led multidisciplinary team (MDT) comprising a consultant or GP with special interest, specialist nurse, specialist dietitian, psychologist, psychiatrist and physiotherapist. In practice these are the specialist weight management clinics that provide non-surgical intensive medical management with an MDT approach. Adults who progress to Tier 4 obesity services usually require hospital-based specialist care, which involves bariatric surgery, supported by an MDT for preoperative assessment and postoperative follow-up. CCGs are responsible for the commissioning of Tier 3 and 4 obesity services.

Table 4 Organisation of obesity services within NHS England (47)

Classification	Management procedures/interventions
Tier 1	Universal services such as health promotion or primary care
Tier 2	Lifestyle intervention
Tier 3	Specialist weight management services
Tier 4	Bariatric surgery

As per NICE clinical guideline on identification, assessment and management of obesity, lifestyle and behaviour management are the cornerstone of general obesity treatment guidelines. The first step in management of obesity is diet and exercise. Pharmacological treatment may be used to maintain weight loss rather than to continue to lose weight. NICE guidelines on general obesity recommend the level of intervention for the patient based on a score-based system described in Table 5, where: (6)

- 1 – General advice on healthy weight and lifestyle
- 2 – Diet and physical activity
- 3 – Diet and physical activity; consider pharmacological intervention
- 4 – Diet and physical activity; consider drugs; consider pharmacological intervention

Table 5 Score-based classification of obesity

Classification	BMI (kg/m^2)	Waist Circumference			Comorbidities
		Low	High	Very high	
Overweight	25-29.9	1	2	2	2
Obesity I	30 – 34.9	2	2	2	2
Obesity II	35 – 39.9	3	3	3	3
Obesity III	>40	4	4	4	4

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Currently, 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. Patients may then be referred for genetic testing, which was initially performed by Prof. Farooqi in Cambridge as part of the GOOS study but is now available through the NHS in England as part of a nationally commissioned service.

With the adoption of setmelanotide by NHS England, there is an opportunity to ensure that genetic testing is performed for patients with severe early onset obesity, rather than trialling lifestyle management, which in these patients

proves ineffective due to the constant drive to eat. Thus, a specific treatment paradigm for genetic obesity should be established, separate to that of general obesity.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

There is currently no clinical pathway for the treatment of RGDOs. Whilst genetic testing is now available and we believe the majority of patients are identified due to the severity of their condition and its very early onset, there are no effective treatment options available. Consequently, patients continue to be exposed to tedious rounds of diet and lifestyle advice whilst continuing to gain weight and remaining at risk of obesity related complications (48).

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

In the UK, setmelanotide would be ideally commissioned based on the proposed model within the National Commissioned Service and managed within “National Expert Centres”, which include:

- All commissioned adult Tier 3 obesity services
- The planned commissioned obesity services (14 planned commissioned paediatric centres according to a discussion with a leading KOL)

Following the implementation of setmelanotide in NHS England the goal would be to send obese patients for genetic testing if their healthcare provider suspects a genetic cause of their obesity, with the main criteria being early onset of obesity (before the age of 5 years) and BMI more than 3 standard deviations above the mean. It has only been recently that genetic testing has become funded as a commissioned service within NHS. It is anticipated that that a national commissioned service will be set up for setmelanotide where all patients will have their treatment initiated at a national expert centre. Once treatment has been initiated by an expert, patients would be referred back to local centres for maintenance treatment. Early diagnosis of early-onset obesity associated with genetic deficiencies is crucial for better management

of the condition and could have a major impact on patient's long-term outcomes, given longer duration of obesity has been linked to poorer outcomes (49-51).

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Setmelanotide will be the only pharmacotherapy indicated for chronic weight management that treats the underlying causes of the conditions, hyperphagia, in adult and paediatric patients 6 years of age and older with obesity due to LEPR or POMC/PCSK1 deficiency confirmed by genetic testing demonstrating variants in the LEPR or POMC genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance(52). Until now, patients with these RGDOs have had to endure ineffective treatments, such as diet and exercise advice, and felt the stigma attached to being obese and their inability to control their eating habits. Setmelanotide represents a step change in that it treats the underlying cause of the disorders and has been shown in clinical trials to reduce hyperphagia and lead to substantial weight gain, with significant impacts for both physical and mental health.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Currently there are no specialised services for patients with genetic obesity due to LEPR or POMC/PCSK1 deficiency as they are managed by SoC, which includes advice on diet and lifestyle management. Genetic testing has only recently become a commissioned service as part of the treatment pathway and all patients with LEPR or POMC deficiency are currently managed by Prof. Farooqi at University of Cambridge Metabolic Research Laboratories. The plan in the future is to refer these patients for genetic testing at University of Cambridge Metabolic Research Laboratories, where an expert will be the key decision maker of whether a treatment with setmelanotide will be initiated. Then patients will be referred back to regional expert centres for continued monitoring of their treatment.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

As per its EMA label, the presence of either biallelic POMC, including PCSK1, deficiency obesity or LEPR deficiency obesity will need to be confirmed by genetic testing demonstrating variants in LEPR, POMC, including PCSK1 genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance. Testing is already available through the NHS in England and patients can already be referred for testing. The main testing criteria are BMI more than 3 standard deviations above the mean, with onset before the age of 5 years, in the absence of significant syndromic features, and with no explanation (53).

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

It is anticipated that the implementation of setmelanotide in NHS England would not require any additional facilities, technologies or infrastructure to be established outside that which is already being established for genetic testing.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Identifying patients with LEPR and POMC obesity and initiating a treatment with setmelanotide as early as possible can help to prevent the accrual of comorbidities associated with obesity, such as joint complications or development of diabetes. This, in turn, would prevent the need for joint replacement surgeries, including all the tests and medical appointments associated with them. If patients' weight and hyperphagia are managed effectively, patients may no longer have to take treatments for the comorbidities associated with obesity (e.g. GLP1 agonists for the treatment of type 2 diabetes). It would also be reasonable to assume that the further long-term benefit of weight loss via setmelanotide is the avoidance of ineffective

anti-obesity therapies, including bariatric surgery, a highly burdensome procedure to both patients and the NHS.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

9.1 Identification of studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature

The objective of the systematic literature review (SLR) was to evaluate the clinical, economic and humanistic evidence associated with the treatment of patients with obesity caused by LEPR or POMC/ PCSK1 deficiency. The SLR was conducted in accordance with the quality standards required by NICE and most health technology agencies and standards set forth in other established guidelines (i.e., Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] and the Cochrane Handbook for Systematic Reviews of Interventions). The SLR was performed in accordance with a predefined protocol documented in Appendix A.

Systematic literature searches of relevant databases were conducted in OvidSP to identify peer-reviewed studies of interest that assess clinical efficacy and safety and health-related quality of life (HRQL) in patients with obesity caused by LEPR or POMC/PCSK1 deficiency.

Databases were searched using a combination of free-text search terms and controlled vocabulary terms specific to each database, as recommended by the Cochrane Collaboration. Search strings were developed using guideline-recommended filters for specific search platforms to identify randomised controlled trials and other clinical studies. Searches were restricted to studies conducted in humans and published in English; no other limits were applied. The databases searched for evidence are listed in Table 6. Search strategies for each database, are provided in Appendix B.

Table 6 Data sources for published studies

Source Type	Data Sources	Platform
Electronic literature databases	Embase MEDLINE and MEDLINE In-Process The Cochrane Library (CENTRAL and CDSR) DARE PsycINFO EconLit	OvidSP
	DARE/HNS EED[1]	CRD

[1] No longer updated; searched to the time of discontinuation.

The search strings were cross-checked with published, peer-reviewed strings from high-quality systematic reviews available relating to the clinical evidence in obesity caused by LEPR or POMC/PCSK1 deficiency, to ensure they captured studies of interest. The literature searches were validated by manual review of the bibliographies of the most recently published, relevant SLRs (i.e., published in the previous 2 years) identified from database searches. The SLRs themselves were not included in the review to avoid double-counting of relevant studies. Additional checks were performed to ensure that recent publications of interest had been captured by the search, to ensure that the SLR completely and comprehensively covered all relevant literature.

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Conference proceedings from 2018 to 2020 were searched to capture emerging evidence that might not have yet been published in peer-reviewed journals (Table 7). It was assumed that studies published as older conference abstracts would have been published and indexed and would therefore be identified by electronic database searches.

Searches were conducted via OvidSP to identify abstracts indexed in Embase.com. For conferences not available in Embase, online conference websites or other relevant media were searched using the keywords shown in Appendix 1 (Table 1).

A supplemental search of clinicaltrials.gov was conducted to identify relevant trials conducted within the previous 5 years, to define ongoing research.

Table 7 Data sources for unpublished studies

Source Type	Data Sources	Platform
Conferences (meeting abstracts)	European Congress of Endocrinology	2018-2019: Available online
	European Conference on Rare Disease and Orphan Products	2018-2020: Available online
	Endocrine Society Annual Meeting	2019: Available online
	European Congress on Obesity	2020: Indexed on Embase
	American Association of Clinical Endocrinologists Annual Congress	2019: Indexed on Embase
Clinical trial registries	Clinicaltrials.gov	
	Orpha.net	

9.2 Study selection

All articles identified through database searches were screened by two independent reviewers to determine eligibility for inclusion. Full-text publications of potentially relevant studies were further reviewed by two independent researchers. At both stages, any conflicts regarding study eligibility were resolved by a third reviewer.

Decisions regarding the eligibility of articles for inclusion in the SLR was based on the population, intervention, comparators, outcomes, and study design (PICOS) criteria outlined in Table 8.

Table 8 Selection criteria for the clinical SLR

	Inclusion criteria	Exclusion criteria
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.	• Patients aged <6 years • Patients with obesity due to other genetic deficiencies or syndromes, or those not meeting age-specific obesity markers • Mixed populations[1] of patients of interest and not of interest for whom the results were not reported separately
Intervention / Comparator	• Setmelanotide in combination with standard management	• orlistat • methylcellulose • bariatric surgery

	Inclusion criteria	Exclusion criteria
Outcomes	• BMI • BMI-Z • Weight • Percent body fat • Waist circumference • Hip circumference • Change in dietary habits • Blood pressure • Hyperphagia • Incidence of obesity comorbidities (e.g., cardiovascular events, type 2 diabetes, cancer, osteoarthritis, sleep apnoea, musculoskeletal pain) • Mortality • Treatment-emergent adverse events • HRQL (patients)	No outcome of interest reported (e.g., pharmacokinetic, pharmacodynamic, genetic/ biomarker, prognostic, or imaging studies, etc.)
Study design	• Clinical trials (single-arm trials, randomised clinical trials, non-randomised trials) • Observational, real-world evidence studies	• Letters to the editor, editorials, comments, opinions, notes, narrative reviews • SLR/meta-analyses/network meta-analyses published in 2018 or earlier • Case studies
Language	English language only	
Search dates		

[1] Studies enrolling a population with various monogenic obesity disorders were eligible for inclusion if ≥80% of the population had a genetic defect of interest. This threshold is in line with Institute for Quality and Efficiency in Health Care recommendations.
[2] Current best supportive care included: behavioural and psychological interventions; strategies including reducing calorie intake and/or increasing physical activity; pharmacological therapies included IMCIVREE, orlistat, and methylcellulose.

Data extraction was performed by one investigator to capture key study details and all outcome variables of interest, and then independently validated by a second investigator. Where multiple (related) publications were identified for a study, these were grouped and data were extracted as one study to avoid double-counting. A third investigator resolved any disagreements. A final check was completed once all information had been extracted to ensure consistency in reporting across publications.

Quality assessments were performed for all interventional studies deemed suitable for inclusion in the SLR. Suitable quality assessment tools were selected based on NICE recommendations: randomised clinical trials were quality assessed using the Cochrane Risk of Bias Assessment Tool 2.0. Observational and single-arm studies were assessed using a modified version of the Critical Appraisal Skills Programme tool, in alignment with recommendations for highly-specialised technologies submissions. Drummond's Quality Assessment Tool was to be used to appraise economic evaluations. Quality assessment was conducted by one reviewer and validated by a second.

Only studies published as full-text articles were deemed suitable for quality assessment because of the lack of detail in abstracts and posters.

9.2.1 Criteria used to select studies from the published literature

Searches for relevant clinical evidence yielded 594 records from electronic literature databases. After the removal of duplicates, there were 579 unique abstracts eligible for title and abstract screening. Of these, 36 publications were identified for full-text screening, 33 of which were excluded. Twenty-six of these articles were case studies or case series, reporting only on case presentation and burden of disease; the case studies/series reports did not present data relating to the effectiveness of setmelanotide or the standard-of-care comparator. The other six studies that were excluded either did not report outcomes of interest, did not include the population of interest or did not include an intervention of interest.

9.2.2 Numbers of published studies

Ultimately, three publications met the PICOS criteria and were eligible for inclusion in the clinical burden of illness SLR. These were Kuhnen 2016 (RM-493-011), Clement 2018 (RM-493-011) and Clement 2020 (RM-493-012 and RM-493-015). Further details are provided in Table 9. Figure 6 presents the selection of studies from the initial search to the final studies included in this review.

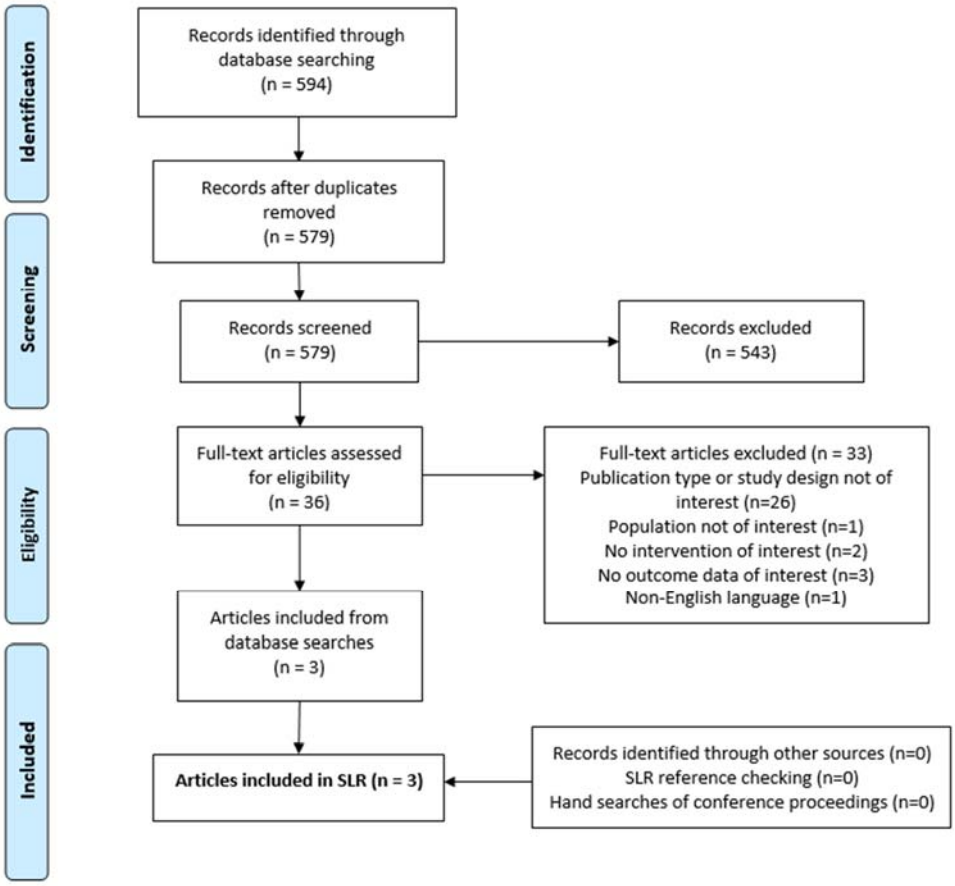


Figure 6 PRISMA flow diagram of findings from the clinical SLR

9.2.3 Criteria used to select studies from the unpublished literature.

Additional unpublished data relevant to this HST were identified by the Sponsor for three clinical studies (RM-493-012, RM-493-015 and RM-493-022). For two of these studies (RM-493-012 and RM-493-015) partial data had already been identified in published articles, during systematic literature review.

- Studies RM-493-012 and RM-493-015 were ongoing at the time of writing the published articles; since then additional data have accrued that are described in updated clinical study reports and are considered unpublished data.
- No data from study RM-493-022 have been published.

9.3 Complete list of relevant studies

9.3.1 Published and unpublished studies identified

Details of all published and unpublished studies identified using the selection criteria are described in Table 9 and Table 10. No drug therapy is approved specifically for the management of obesity and hyperphagia associated with POMC/PCSK1 or LEPR deficiency. The comparator used for modelling is standard management/best supportive care; no unpublished studies compared setmelanotide directly with best supportive care.

Three published articles describing the efficacy and safety of interventions for the treatment of obesity and/or hyperphagia caused by LEPR or POMC/ PCSK1 genetic defects were identified by the SLR (Table 9). Reports were based on studies that investigated setmelanotide; no published evidence on the efficacy and safety of relevant treatment comparators or standard of care was identified by the SLR.

Table 9 List of relevant published studies

Data source	Article title (acronym)	Population	Intervention	Comparator
Kühnen 2016 (54)	Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist (Study RM-493-011)	Obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway	Setmelanotide	None
Clément 2018 (27)	MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency (Study RM-493-011)	POMC-homozygous, heterozygous, and epigenetic deficiency LEPR deficiency	Setmelanotide	None
Clément 2020 (55)	Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, Phase 3 trials (Studies RM-493-012 and RM-493-015)	POMC deficiency obesity due to biallelic, loss-of-function POMC or PCSK1 gene mutations	Setmelanotide	Included a placebo controlled withdrawal period

Published data from studies RM-493-012 and RM-493-015 describe early study findings (55). However, more recent, complete data are available in updated clinical study reports that are presented as unpublished studies (Table 10); one additional clinical study report, for trial RM-493-022, also provides recent and unpublished data on the long-term efficacy of setmelanotide.

Table 10 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Kühnen, 2021 (clinical study report)(56)	An open-label, 1-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide (RM-493), a melanocortin 4 receptor (MC4R) agonist, in early onset POMC deficiency obesity due to bi-allelic loss-of -function POMC or PCSK1 genetic mutation (Study RM-493-012)	POMC deficiency obesity due to biallelic, loss-of-function POMC or PCSK1 gene mutations	Setmelanotide	Placebo
Wabitsch, 2021 (clinical study report)(56)	An open-label, 1-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide (RM-493), a melanocortin 4 receptor (MC4R) agonist, in leptin receptor (LEPR) deficiency obesity due to bi-allelic loss-of-function LEPR genetic mutation (Study RM-493-015)	Bi-allelic, 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 a severe obesity phenotype	Setmelanotide	Placebo
Kühnen, 2020 (clinical study report)(56)	Long-term extension trial of setmelanotide (RM-493) 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 (Study RM-493-022)	Obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway	Setmelanotide	None

9.3.2 Rationale for excluding any study listed in Table 9 and Table 10

Study RM-493-011 was an investigator-initiated proof-of-concept study which formed the basis of the protocols for RM-493-012 and RM-493-015. Data from study RM-493-011 have not been used in the modelling as it included a very small sample of patients and was superseded by the Phase 3 studies that had both a larger sample size, making the results more generalisable and also reported BMI change over a longer period of time (52 weeks). Whilst up to 5.5 years' of follow up time was available for one patient (unpublished data) from study RM-493-011 for POMC patients, interpretation of the results in aggregate was confounded by dose titration and a lack of reporting on data required to calculate BMI change.

9.4 Summary of the methodology of relevant studies

9.4.1 Study design and methodology for published and unpublished studies

Published studies

Three published interventional studies were identified by the SLR and all three investigated the efficacy and safety of setmelanotide for the treatment of obesity and/or hyperphagia caused by genetic LEPR or POMC/ PCSK1 defects (Table 11).

An investigator-initiated, Phase 2 study (RM-493-011) enrolled 2 patients with POMC mutations and 3 patients with LEPR mutations across Germany, France and the UK. In study RM-493-011 patients were dose-escalated to their optimal individualised dose to a maximum dose of 2.5 mg per day and their treatment duration ranged from 122 to 611 weeks.

Two single-arm, Phase 3 trials further investigated the efficacy and safety of setmelanotide in larger groups of patients with severe obesity caused by POMC (RM-493-012) or LEPR (RM-493-015) deficiency. At the time of the publication, the two international trials had recruited 10 patients with POMC and 11 patients with LEPR mutations from databases and genetic obesity registries. The primary endpoint was percent change in weight from baseline.

In the Phase 3 trials, adult patients received a setmelanotide starting dose of 1 mg per day that was up-titrated to achieve an individualised therapeutic dose; paediatric patients received a starting dose of 0.5 mg per day and was similarly up-titrated. Participants who reached the target weight loss threshold by Week 12 of treatment entered a double-blind, placebo-controlled withdrawal period, to receive setmelanotide or placebo-control for 4 weeks. After completion of the withdrawal phase, patients returned to the previously established setmelanotide dose for a further 32 weeks. Over the entire 52-week study period, patients received active setmelanotide treatment for a total of 48 weeks. The primary endpoint was the proportion of patients with 10% reduction in weight from baseline.

Table 11 Methodology used for published studies

	RM-493-012	RM-493-015	RM-493-011	
	Clément 2020 (55)		Kühnen 2016 (54)	Clément 2018 (27)
NCT/registration number	NCT02896192	NCT03287960	NCT02507492	
Study objectives	To evaluate the MC4R agonist setmelanotide in individuals with severe obesity due to:		To present experience using the MC4R agonist, setmelanotide, to treat severe obesity and hyperphagia in two patients with POMC deficiency	To test whether setmelanotide treatment of individuals with LEPR deficiency might result in reductions in hunger and body weight
	POMC deficiency	LEPR deficiency obesity		
Location	International		Germany	France, UK
Study design	Phase 3, single-arm, open-label, multicentre		Phase 2, single-arm, open-label pilot	Phase 2, single-arm
Study duration	2017 to 2018	2017 to 2018	Not reported	
Duration of follow-up	52 weeks	52 weeks	42 weeks	30 to 61 weeks
Study inclusion criteria	Individuals aged ≥6 years with obesity caused by		Adult patients with POMC deficiency, with extreme early-onset obesity and hyperphagia.	Individuals with confirmed homozygous loss-of-function mutations in LEPR.
	POMC deficiency (homozygous or compound heterozygous variants in POMC or PCSK1)	LEPR deficiency (homozygous or compound heterozygous LEPR variants)		
	with a BMI of ≥30 kg/m² (for those aged ≥18 years) or bodyweight of >95th percentile for age on a growth chart (for those aged ≥6 to <18 years).			
Study exclusion criteria	A recent diet and/or exercise regimen resulting in weight loss or stabilisation; previous gastric bypass surgery resulting in >10% weight loss with no evidence of weight regain.		Not reported	
Total sample size	15	15	2	3

	RM-493-012	RM-493-015	RM-493-011	
Study intervention	Setmelanotide		Setmelanotide	
Participant follow-up, duration of follow-up, lost to follow-up	Not reported		Not reported	
Statistical tests	Primary endpoint: an exact binomial test at a one-sided α level of 0·05 Secondary endpoints: a linear mixed-effect model		Descriptive statistics	
Primary outcomes (including scoring methods and timings of assessments)	Proportion of participants achieving ≥10% weight loss from baseline to ~1 year. All endpoints assessed after ~1 year at the therapeutic dose (based on Week 52 data, following 48 weeks of setmelanotide at the individualised therapeutic dose and 4 weeks of placebo).		Percent change in body weight and BMI from baseline. Patient outcomes were reported at various timepoints	
Secondary outcomes (including scoring methods and timings of assessments)	After ~1 year at the therapeutic dose: mean percent change in body weight; mean percent change in 'most hunger' score on an 11-point Likert-type scale in participants aged ≥12 years; proportion of participants who achieved ≥25% reduction in 'most hunger' score; change in waist circumference, metabolic parameters, and percent change in body fat mass. The proportion of participants with 5%, 15%, 20%, 25%, 30%, 35%, and 40% weight loss from baseline Reversal of weight gain and hunger reduction during the placebo-controlled withdrawal sequence Safety and tolerability of setmelanotide.		Change from baseline in: resting energy expenditure (and per kg body weight, per unit lean body mass) lean body mass, fat mass, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, triglycerides, lipoprotein, glycated haemoglobin (HbA1c), insulin-like growth factor, leptin, fasting insulin, fasting glucose, luteinising hormone, follicle stimulating hormone, hunger score on an 11-point Likert scale Patient outcomes were reported at various timepoints	Change from baseline in: hyperphagia score, oral glucose tolerance test, the gonadotropin-releasing hormone test, full blood count, serum lipids, liver and kidney function, leptin, insulin-like growth factor; body composition; energy expenditure; dermatological examination; psychological evaluation every three months Patient outcomes were reported at various timepoints

Unpublished data

Detailed study design and methodology for the two pivotal, placebo-controlled studies conducted with setmelanotide are presented in Table 12. In addition to providing additional data on top of what is provided in the publications identified through the SLR, the unpublished data relating to these studies also includes data from additional supplemental patients. The unpublished data from these two studies has therefore been presented here for completeness.

The two studies had identical design being primarily open-label, with an 8-week withdrawal period that included 4 weeks of placebo-dosing period that occurred at a variable time during the 8 weeks; study personnel and participants were blinded as to the timing of placebo dosing. The placebo-controlled withdrawal period allowed each patient to serve as their own control. Study RM-493-012 enrolled POMC/PCSK1 deficiency patients and study RM-493-015 enrolled LEPR deficiency patients.

Table 12 Methodology used for Studies RM-493-012 and RM-493-015

	Study RM-493-012 (56)	**Study RM-493-015 (56)**
Study title	An open-label, 1-year trial, including a double-blind placebo-controlled withdrawal period, of setmelanotide (RM-493), a melanocortin 4 receptor (MC4R) agonist,	
	in early-onset POMC deficiency obesity due to bi-allelic loss-of-function POMC or PCSK1 genetic mutation	in leptin receptor (LEPR) deficiency obesity due to bi-allelic loss-of-function LEPR genetic mutation
Objectives	**Primary**: To demonstrate statistically significant and clinically-meaningful effects for treatment with setmelanotide on percent body weight change at the end of 1 year of treatment. **Secondary**: To assess the effect of setmelanotide treatment over 1 year on: • Safety and tolerability (including blood pressure and heart rate). • Hunger for patients ≥12 years of age. • Percent change in body fat mass. • Glucose parameters: fasting glucose, HbA1c, and oral glucose tolerance test (OGTT) with a focus on parameters of insulin sensitivity. • Waist circumference. • Reversal of weight and hunger reduction during the double-blind, placebo-controlled withdrawal period.	

	Study RM-493-012 (56)	Study RM-493-015 (56)
	Tertiary: to assess the effect of setmelanotide treatment over 1 year on: • Percent change in total body mass, non-bone lean mass, and bone density. • Fasting lipid (cholesterol and triglyceride) panel. • Setmelanotide pharmacokinetics. • C-reactive protein. • Dose response of setmelanotide through titration. • Change in quality of life and health status. **Exploratory**: to assess the effect of setmelanotide treatment over 1 year on: • Hunger in patients aged 6 to 11 years. • Changes in neurocognition in patients aged 6 to 16 years. • Change in pubertal development for patients yet to reach Tanner Staging V. • Change in growth and development as assessed by bone age. • Ambulatory blood pressure measurement, skin pigmentation, energy expenditure, and 24-hour pharmacokinetic profile (for patients participating in optional sub-studies). • Hormonal, neuroendocrine, metabolic and anti-inflammatory analytes and biomarker assays. • Any pharmacokinetic/pharmacodynamics response (employing a suitable endocrine biomarker predictive of setmelanotide target engagement, agonism and efficacy through activation of MC4R).	
	• Correlation of bi-allelic or loss-of-function POMC and PCSK1 genetic mutations and POMC deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy.	• Correlation of bi-allelic or loss-of-function LEPR genetic mutations and deficiency due to diverse allelic variants with the magnitude of setmelanotide efficacy.
Location	A multicentre study conducted in Germany, the UK, France, Canada, the USA, Spain and Belgium	A multicentre study conducted in Germany, France, the Netherlands and the United Kingdom
Design	These Phase 3 studies both began with an initial 2- to 12-week dose-titration period (duration dependent upon number of dose escalations required to reach the individual's therapeutic dose). During dose titration, the setmelanotide dose was increased by 0.5 mg every second week up to the individual's therapeutic dose or to the approved maximum dose. Thereafter, patients continued active treatment at their optimal therapeutic dose for an additional 10 weeks (a total duration of 12 weeks at the individual patient's therapeutic dose). Patients who achieved ≥5 kg weight loss (or ≥5% loss if baseline body weight was <100 kg) by the end of the open-label treatment period, continued into the double-blind, variably-timed, placebo-controlled, 8-week withdrawal period (which included a 4-week	

	Study RM-493-012 (56)	Study RM-493-015 (56)
	placebo period). The onset of the placebo period was variable for each patient in order to mask the actual timing of setmelanotide withdrawal. Following the withdrawal period, patients went on to complete approximately 1 year of treatment at the therapeutic dose.	
Duration of study	Total study duration was approximately 16.5 months. Initial treatment over 12 to 22 weeks (12 weeks at the therapeutic dose), followed by an 8-week placebo-controlled withdrawal period for patients with sufficient weight loss, and then a 32-week open-label treatment period at the individual patient's therapeutic dose. The primary endpoint was assessed 52-weeks after the patient achieved their individualised therapeutic dose	
Sample size	15 patients	15 patients
Inclusion criteria	Patients were required to fulfil the following criteria:	
	1) Have bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for the POMC or PCSK1 genes, with the loss-of-function variant for each allele conferring a severe obesity phenotype.	1) Have bi-allelic, homozygous or compound heterozygous (a different gene mutation on each allele) genetic status for the LEPR gene, with the loss-of-function variant for each allele conferring a severe obesity phenotype.
	2) Be aged ≥6 years. 3) Adults aged ≥18 years, were to be obese with a BMI of ≥30 kg/m^2; children or adolescents were to be obese with BMI ≥95th percentile for age. 4) The study participant or parent/guardian was to be able to communicate well with the investigator, understand and comply with the requirements of the study, and understand and sign the written informed consent after being informed about the study. 5) Female participants of child-bearing potential were to agree to use contraception. 6) Male participants with female partners of child-bearing potential were to agree to use a double barrier-method of contraception if sexually active during the study. Male patients were not to donate sperm during the study or for 90 days after.	
Exclusion criteria	The following were reasons for exclusion from the study: 1) A recent (within 2 months) intensive diet and/or exercise regimen with or without use of weight-loss agents, including herbal medications, that resulted in weight loss or stabilisation. 2) Prior gastric bypass surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain. Patients could be considered if surgery was unsuccessful, resulted in <10% weight loss, or there was clear evidence of weight regain after an initial response to bariatric surgery. 3) A diagnosis of schizophrenia, bipolar disorder, personality disorder or other Diagnostic and Statistical Manual of Mental	

	Study RM-493-012 (56)	Study RM-493-015 (56)
	Disorders (DSM-III) disorder that the investigator believed would interfere significantly with study compliance. 4) A Patient Health Questionnaire-9 (PHQ-9) score of ≥15. 5) Suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). A lifetime history of a suicide attempt or suicidal behaviour in the last month. 6) Current, severe stable restrictive or obstructive lung disease due to extreme obesity, evidence of significant heart failure (New York Heart Association [NYHA] Class ≥3) or oncologic disease if severe enough to interfere with the study and/or likely to confound the results. 7) A history of significant liver disease/injury or current liver assessment for a cause of abnormal liver tests for an aetiology other than non-alcoholic fatty liver disease (NAFLD). Any liver aetiology besides NAFLD required exclusion from the study (including diagnosed non-alcoholic steatohepatitis [NASH], other causes of hepatitis, or a history of hepatic cirrhosis). 8) A history or the presence of impaired renal function as indicated by clinically-significant abnormal creatinine, blood urea nitrogen, or urinary constituents (e.g., albuminuria) or moderate to severe renal dysfunction as defined by a Cockcroft Gault equation of <30 mL/min. 9) A history or close family history of skin cancer or melanoma, or a patient history of ocular-cutaneous albinism. 10) Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions, determined on comprehensive skin evaluation by a qualified dermatologist. Any lesions of concern were biopsied and confirmed as benign prior to enrolment; if pre-treatment biopsy results were of concern, the patient could be excluded from the study. 11) The patient was, in the opinion of the study investigator, not suitable to participate in the study. 12) Participation in any clinical study with an investigational drug/device within the 3 months prior to the first day of dosing.	
	13) Significant hypersensitivity to study drug	13) A history of significant hypersensitivity to study drug/ exogenously injected peptides.
	14) Inability to comply with a once-daily injection regimen. 15) Placement in an institution through an official or court order, or dependence on the sponsor, investigator or study site.	
Method of randomisation	These were non-randomised studies.	
Method of blinding	The study was open-label, except for the 8-week double-blind, placebo-controlled, variably-timed withdrawal period. The placebo formulation was a study drug-matched solution for injection, comprising setmelanotide vehicle. The Investigator, study site staff, site management and medical monitor did not know the treatment sequence for the 8-week, double-blind, placebo-controlled phase.	

	Study RM-493-012 (56)	Study RM-493-015 (56)
Intervention and comparator	The setmelanotide drug product was a sterile solution for subcutaneous injection, at a concentration of 10.0 mg/mL. Setmelanotide was administered by once-daily injection at doses of 0.5 mg to 3.0 mg. The maximum allowable dose differed across countries based on feedback from competent authorities; the US, UK, Canada and the Netherlands authorities approved a maximum daily dose of 3.0 mg, while the German and French authorities approved a maximum daily dose of 2.5 mg. The starting dose was 0.5 mg for paediatric/adolescent patients and 1.0 mg for adults; dose titration was conducted with the potential for dose increase of 0.5 mg every second week for up to 12 weeks. Patients were assessed every second week for weight loss and suppression of hunger symptoms. A weight loss for adults of 2 to 3 kg per week and a reduction in hunger scores to between 0 and 2 indicated that the patient had achieved their therapeutic dose; a weight loss for adolescents and children of 1 to 2 kg per week and a reduction in hunger scores to between 0 and 2 indicated that the patient had achieved their therapeutic dose. Once the individual patient's therapeutic dose was achieved, the same dose was administered for the remainder of the study. Placebo comprised setmelanotide vehicle and was administered for 4 weeks during the double-blind withdrawal period.	
Baseline differences	As all patients received both study drug and placebo, baseline differences are not applicable to the study population.	
Duration of follow-up, lost to follow-up information	Patients were to receive a total of 52-weeks of treatment with their individualised setmelanotide dose; after completing the pivotal study they were eligible to enrol in a separate long-term extension study to continue receiving setmelanotide (Study RM-493-022) or they completed a final study visit approximately 30 days after their last dose.	
	The clinical study report of 07 May 2021 includes data for 15 patients, who were administered at least 1 setmelanotide dose. Ten patients were classified as part of the pivotal cohort and the other 5 patients were deemed supplemental. In the pivotal cohort 9 of 10 patients completed 52 weeks of setmelanotide treatment and 1 patient withdrew due to lack of treatment efficacy. In the supplemental cohort 3 patients completed the study and 2 patients withdrew. One patient was lost to follow up.	The clinical study report of 12 May 2021 includes data for 15 patients, who were administered at least 1 setmelanotide dose. Eleven patients were classified as part of the pivotal cohort and the other 4 patients were deemed supplemental. In the pivotal cohort 9 of 11 patients completed the full 12 months of setmelanotide treatment and 2 patients withdrew. In the supplemental cohort 4 patients completed the study. No patients were lost to follow up.
Statistical tests	The primary endpoint was the proportion of patients in the Full Analysis Set (FAS) who demonstrated at least 10% weight reduction at ~1 year (10 to 14 months post-baseline) compared	

	Study RM-493-012 (56)	Study RM-493-015 (56)
	with baseline. The FAS comprised all patients who received study drug and had at least one baseline assessment. The null hypothesis was that the proportion would be ≤5% and the alternative hypothesis was that the proportion would be >5%. This was analysed using an exact binomial test, at a 1-sided 5% significance level; corresponding 2-sided 90% confidence intervals (CIs) were calculated using the exact Clopper-Pearson method. The first key secondary efficacy endpoint was the percent change from baseline in body weight at the end of approximately 1 year of treatment. It was analysed using the Designated Use Set (DUS), which comprised patients who received study drug, demonstrated loss of ≥5 kg or ≥5% (if baseline weight was <100 kg) in body weight over the 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period. The second key secondary efficacy endpoint was the mean percent change from baseline in weekly average hunger (using "most hunger over the last 24 hours" daily response) in the DUS (for patients aged 12 years and older). A linear mixed-model repeated-measures analysis of variance (ANOVA) with a fixed term for time and baseline and a random effect for patients was planned to assess the first and second secondary efficacy endpoints; however, if there were insufficient data points a longitudinal mixed model could be used. An unstructured covariance matrix was used to model the expected different variances among participants. In the event the mixed model did not converge with an unstructured covariance matrix; a compound-symmetric then Toeplitz covariance matrix was to be employed. The third key secondary endpoint was the proportion of patients in the FAS who achieved at least a 25% reduction in hunger from baseline at the end of approximately 1-year of treatment. The exact binomial test was used to test whether the percentage of patients with at least 25% hunger improvement was >5%.	
Primary outcomes	The primary endpoint was the proportion of patients in the FAS who met the ≥10% weight loss threshold (responders) after approximately 1 year (52 weeks) of treatment, compared with the proportion reported in historical data (at most, 5% responders in the null population).	
Secondary outcomes	Key secondary endpoints assessed were: 1. Mean percent change in body weight from baseline in the DUS. 2. Mean percent change in weekly average daily hunger score ('most hunger over the last 24-hours') from baseline in patients aged ≥12 years in the DUS. 3. A responder threshold of ≥25% improvement from baseline in hunger in the FAS. Other secondary endpoints were: • The safety and tolerability of setmelanotide treatment. • Daily hunger score throughout the study; patients aged ≥12 years self-reported hunger by responding to three questions; patients aged 6 to 11 years self-reported hunger	

	Study RM-493-012 (56)	Study RM-493-015 (56)
	each morning just prior to dosing by responding to one question. • Two global hunger questions were administered to assess patient perception of their current status and change from baseline. • Glucose parameters as measured by fasting glucose, HbA1c and OGTT with a focus on parameters of insulin sensitivity. • Waist circumference according to US National Heart Lung and Blood Institute criteria over the course of the study. • Improvement in weight and hunger, with a placebo withdrawal period implemented to allow each patient to serve as their own control.	

Study RM-493-022 was a long-term extension study with the primary aim of assessing the safety and tolerability of setmelanotide. Patients had all participated in a previous trial of setmelanotide. Details of the methodology are provided in Table 13.

Table 13 Summary of methodology for Study RM-493-022 (56)

Study name	Long-term extension trial of setmelanotide (RM-493) 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
Objectives	**Primary**: To characterise the safety and tolerability of setmelanotide in patients who had completed treatment in a previous trial of setmelanotide for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. **Exploratory**: To assess the effect of long-term setmelanotide treatment on: • Maintained or continued weight loss • Hunger • Percent change in body fat mass • Waist circumference • Percent change in total body mass, non-bone lean mass, and bone density • Fasting lipid (cholesterol and triglyceride) panel • Changes in quality of life and health status • Biomarkers predictive of a setmelanotide response and/or that change when the rate of weight loss may change later in the treatment regimen.
Location	A multicentre study conducted in Germany, the US and Canada.
Design	This was a Phase 3, open-label extension study of up to an additional 2 years' treatment with setmelanotide for patients who

	had completed a prior setmelanotide study for genetic obesity disorders with a mutation upstream of the MC4 receptor in the melanocortin-leptin pathway. Assessment of safety used the same parameters as the main studies, to allow all patients (regardless of the disease under study) to be assessed in a single extension study. As far as was possible, qualifying patients were to be enrolled immediately on completion of their main study to avoid any interruption in setmelanotide treatment. Patients continued taking the same setmelanotide dose as administered on completion of their main study. Dose level changes were allowed at any time based on safety or efficacy findings.
Duration of study	This extension study was to provide up to an additional 2 years of setmelanotide treatment.
Sample size	All patients included were required to have completed one year of setmelanotide therapy in one of the two Phase 3 clinical trials. Thus, sample size estimation and power analyses were not relevant. A total of 15 patients were enrolled in the extension study. As of the baseline freeze date (09 May 9 2019) data for 7 POMC/PCSK1 patients was available. A report rider dated April 30, 2020 provided data for an additional 2 POMC/PCSK1 patients. No data on LEPR patients was available at baseline freeze but 6 LEPR patients were included in the report rider
Inclusion criteria	Patients were required to fulfil the following criteria: 1) Be ≥6 years of age and have completed participation in and demonstrated adequate safety in a previous setmelanotide study for obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway. 2) The participant and/or parent or guardian was able to communicate well with the investigator, understand and comply with study requirements, and to understand and sign written informed consent/assent. 3) Female participants of child-bearing potential were to agree to use contraception. A female participant who had not reached menarche on study entry but was suspected to have subsequently achieved this status was to promptly inform the investigator and undergo pregnancy testing.
Exclusion criteria	The following were reasons for exclusion from the study: 1) Current, clinically significant disease, severe enough to interfere with the study and/or confound the results. 2) Pregnancy and/or breastfeeding. 3) Diagnosis of schizophrenia, bipolar disorder, personality disorder or other DSM-III disorders that the investigator believed would interfere significantly with study compliance. 4) A PHQ-9 score of ≥15. 5) Any suicidal ideation of type 4 or 5 on the C-SSRS. Any lifetime history of a suicide attempt, or any suicidal behaviour in the last month. 6) Current, severe, stable, restrictive or obstructive lung disease as a consequence of extreme obesity; evidence of

	significant heart failure (NYHA Class 3 or greater); or oncologic disease severe enough to have interfered with the study and/or confound the results. 7) History of significant liver disease or liver injury, or current liver assessment for a cause of abnormal liver tests for an aetiology other than NAFLD. Thus, any underlying aetiology besides NAFLD, including diagnosed NASH, other causes of hepatitis, or history of hepatic cirrhosis were exclusionary; the presence of NAFLD was not exclusionary. 8) History or presence of impaired renal function. 9) History or close family history (parents or siblings) of skin cancer or melanoma, or patient history of ocular-cutaneous albinism. 10) Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions 11) The patient was, in the opinion of the study investigator, not suitable to participate in the study. 12) Significant hypersensitivity to the study drug. 13) Inability to comply with the injection regimen. 14) Patients who had been placed in an institution through an official or court order, or who were dependent on the sponsor, investigator or study site.
Method of randomisation	This was a non-randomised study.
Method of blinding	This was an open-label study, with no blinding conducted.
Intervention (n = 15)	The setmelanotide drug product was a sterile solution for subcutaneous injection, at a concentration of 10.0 mg/mL. Setmelanotide was administered by once-daily injection at the same dose (0.5 mg to 3.0 mg) as administered at the end of participation in the main study. Dose changes were permitted to optimise safety/tolerability and efficacy. Downward titration was allowed after discussion with the Sponsor. If dose increase was deemed necessary, the patient was to remain under observation for approximately 3 hours after the first higher dose was administered. Dose adjustments were made in increments of 0.5 mg. The maximum dose permitted differed between countries based on recommendations from competent authorities. At the time this study was conducted the US and Canada had approved a maximum daily dose of 3.0 mg, while Germany had approved a maximum daily dose of 2.5 mg.
Baseline differences	As all patients received study drug, baseline differences are not applicable to the study population.
Duration of follow-up, lost to follow-up information	The clinical study report includes data for 16 patients, who were administered at least 1 setmelanotide dose. Seven patients were from Study RM-493-012 and the other 9 patients were from study RM-493-014 (an open-label, Phase 2 study of ~52 weeks of setmelanotide treatment in patients with rare genetic obesity disorders) and had various genetic mutations. The clinical study

	report of March 2020 presents data for the 7 patients from Study RM-493-012 who had a POMC mutation. At the time of writing the clinical study report, all 7 POMC patients remained on study and none had discontinued. No patients were lost to follow up.
Statistical tests	As this patient group is extremely rare, efforts were made to include all data in all endpoint analyses. No missing data were imputed and analyses were conducted on all available data. With respect to exploratory endpoints, no adjustment for multiplicity were included for assessment of rare genetic obesity populations. Safety and efficacy data from both the man and extension studies could combined to evaluate long-term safety and efficacy outcomes on a patient-specific and population basis.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the safety and tolerability of setmelanotide, assessed by the frequency and severity of adverse events; changes in physical examination, electrocardiogram (ECG), vital sign, and laboratory evaluations; and the occurrence of injection site reactions.
Secondary outcomes (including scoring methods and timings of assessments)	No secondary endpoints were specified for this study. Exploratory endpoints included: • The yearly mean percent change from baseline in body weight. • Hunger, assessed at each visit using a daily questionnaire and 2 global questions. • Yearly body composition including total body weight loss, fat loss, and non-bone lean mass. • Waist circumference was measured according to United States National Heart Lung and Blood Institute criteria. • Potential improvements in lipid levels (fasting cholesterol and triglycerides) were assessed over time. • Quality of life was assessed yearly using the validated self-reporting instruments Impact of Weight on Quality of Life-Lite (IWQOL-Lite) specific for obesity for participants aged ≥18 years and the measurement model for the Pediatric Quality of Life Inventory (PedsQL) for participants aged <18 years. The validated self-reporting instrument SF-36 or SF-10 were used to measure functional health and well-being. • Biomarkers predictive of a setmelanotide response and/or that change when the rate of weight loss may change later in treatment could be evaluated using metabolic biomarkers. Such pharmacodynamic markers could include neuroendocrine and endocrine indicators of energy metabolism (e.g. ghrelin, leptin, insulin, orexin, and oxytocin, peptide YY, glucagon-like peptide-1, melanocyte stimulating hormone, pro-insulin, adrenocorticotropic hormone, brain-derived neurotrophic factor) or anti-inflammatory markers such as high-sensitivity C reactive protein.

9.4.2 Details on data from any single study that has been drawn from more than one source

The published studies identified by the SLR reported partial, early data from the initial analyses of trials RM-493-012 and RM-493-015 (55).

The full dataset for trials RM-493-012 and RM-493-015 and/or more recent data accrued since writing the published articles, are available in the format of clinical study reports (dated May 2021) that are identified as unpublished studies (56).

9.4.3 Differences between patient populations and methodology between studies

9.4.3.1 ***Published studies***

Patient populations

The three study populations were generally comparable with respect to age, ranging from 11 to 37 years. Participants in RM-493-012 (POMC/PCSK1 patients) were, on average, slightly older than those enrolled in RM-493-015 (LEPR patients) (mean age: 23.7 years vs. 18.4 years)(55). Studies RM-493-011(27, 54) and RM493-015(55) comprised a higher proportion of female patients, while study RM-493-012 comprised an equal proportion of males and females.

The average baseline BMI was somewhat higher in patients enrolled in the Phase 3 LEPR trial compared with the POMC/PCSK1 trial (48.2 kg/m^2 vs. 40.4 kg/m^2), reflecting the often more severe nature of LEPR deficiency. Baseline hunger scores were reported as markedly severe for all studies: patients in the Phase 2 trial reported the highest baseline hunger scores (>9); patients in the Phase 3 POMC/PCSK1 trial reported higher baseline hunger scores than LEPR trial population (8.0 vs. 7.1). Commonly reported premorbid conditions included adrenocorticotropic hormone deficiency, hypothyroidism and type 1 diabetes in the POMC population; hypogonadotropic hypogonadism in the LEPR population; and type 2 diabetes in both the LEPR and POMC populations.

9.4.3.2 *Unpublished studies*

Patient populations

Patients enrolled into setmelanotide clinical studies had homozygous (identical gene mutations on each allele) or compound heterozygous (a different gene mutation on each allele) genetic status for the POMC/PCSK1 (RM-493-012) or LEPR (RM-493-015) genes with the loss-of-function variant for each allele conferring a severe obesity phenotype. Long-term treatment data from Study RM-493-022 considers any patients who had completed a trial of setmelanotide for the treatment of obesity associated with any genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, however, only patients with relevant POMC/PCSK1 or LEPR deficiencies are included in this submission.

Inclusion criteria stipulated that patients should be ≥6 years old. Five patients treated in Study RM-493-012 were aged <12 years; 1 patient treated in Study RM-493-015 was aged ≤12 years.

Studies RM-493-012 and RM-493-015 required that adults had a BMI of ≥30 kg/m^2 and that children/adolescents had a BMI of ≥95% of the percentile for age (55). Study RM-493-022 did not specify a BMI but patients entering the long-term treatment study had already participated in 1 year of setmelanotide dosing in their initial study (56).

Studies RM-493-012, RM-493-015 and RM-493-022 all required that patients had a PHQ-9 score of ≥15.

Other enrolment criteria were broadly consistent between studies.

Study RM-493-012

In the pivotal cohort, five (50%) of the 10 patients were male and five (50%) were female. The median age of the patients was 16.5 years (range 11-30 years). There were 2 patients younger than 12 years (both 11 years). The mean BMI at inclusion was 40.41 kg/m^2 corresponding to class III, massive or morbid obesity (55).

The main characteristics of the 5 patients included in the supplemental cohort were as follows: 4 patients were male, the median age was 11 years (range, 7 to 29 years), of which 3 patients were younger than 12 years, and the mean BMI at inclusion was 36.68 kg/m^2 corresponding to class II or severe obesity. Table 14 presents the characteristics of patients on inclusion into Study RM-493-012.

Table 14 Patient characteristics on inclusion in Study RM-493-012 (SAS) (55)

	Pivotal cohort (N=10)	**Supplemental cohort (N=5)**	**Total (N=15)**
Age at inclusion (years)			
n	10	5	15
Average (standard deviation)	18.4 (6.17)	14.80 (8.73)	17.20 (7.02)
Median	16.5	11.00	16.00
Q1, Q3	15, 22	10.00, 17.00	11.00, 22.00
Min, Max	11, 30	7.0, 29.0	7.0, 30.0
Age group, n (%)			
< 12 years old	2 (20.0)	3 (60.0)	5 (33.3)
≥ 12 years	8 (80.0)	2 (40.0)	10 (66.7)
Gender n (%)			
Male	5 (50.0)	4 (80.0)	9 (60.0)
Woman	5 (50.0)	1 (20.0)	6 (40.0)
Ethnicity, n (%)			
Caucasian	7 (70.0)	1 (20.0)	8 (53.3)
Other	3 (30.0)	4 (80.0)	7 (46.7)
Arabic	1 (10.0)	1 (20.0)	2 (13.3)
Moroccan	1 (10.0)	0	1 (6.7)
Turkish	0	2 (40.0)	2 (13.3)
Not applicable	1 (10.0)	0	1 (6.7)
Not carried forward	0	1 (20.0)	1 (6.7)
Ethnicity, n (%)			
Hispanic or Latin	1 (10.0)	1 (20.0)	2 (13.3)
Non-Hispanic and non-Latin	8 (80.0)	3 (60.0)	11 (73.3)
Unknown	1 (10.0)	1 (20.0)	2 (13.3)
Country			
United States	1 (10.0)	0	1 (6.7)
France	1 (10.0)	1 (20.0)	2 (13.3)
Germany	7 (70.0)	0	7 (46.7)
Canada	1 (10.0)	0	1 (6.7)
Spain	0	2 (40.0)	2 (13.3)
Belgium	0	2 (40.0)	2 (13.3)
Genotyping, n (%)			
POMC	9 (90.0)	4 (80.0)	13 (86.7)
PCSK1	1 (10.0)	1 (20.0)	2 (13.3)
Weight			
n	10	5	15
Average (standard deviation)	118.7 (37.5)	96.37 (30.10)	111.26 (35.81)

	Pivotal cohort (N=10)	Supplemental cohort (N=5)	Total (N=15)
Median	114.950	100.50	114.40
Q1, Q3	106.30, 139.10	83.67, 104.00	83.67, 138.00
Min, Max	55.87, 186.73	55.7, 138.0	55.7, 186.7
Size (cm)			
n	10	5	15
Average (standard deviation)	169.6 (13.96)	160.20 (14.02)	166.47 (14.23)
Median	170.0	156.00	167.00
Q1, Q3	159, 175	156.00, 165.00	156.00, 175.00
Min, Max	145, 195	143.0, 181.0	143.0, 195.0
BMI (kg/m^2)			
n	10	5	15
Average (standard deviation)	40.41 (9.048)	36.68 (6.34)	39.17 (8.21)
Median	40.99	36.91	39.40
Q1. Q3	33.8, 49.1	34.38, 42.12	33.79, 43.67
Min, Max	26.6, 53.3	27.2, 42.7	26.6, 53.3
Waist circumference (cm)			
n	10	5	15
Average (standard deviation)	121.80 (18.955)	110.66 (17.35)	118.09 (18.62)
Median	122.50	109.30	121.00
Q1. Q3	112.0, 128.0	103.00, 122.00	104.00, 128.00
Min, Max	86.0, 150.0	87.0 ; 132.0	86.0, 150.0

Study RM-493-015

In the pivotal cohort, 8 of the 11 patients (72.7%) were female and 3 (27.3%) were male. The median age of the patients was 23 years (range 13 to 37 years). The mean BMI at inclusion was 48.17 kg/m^2 corresponding to class III, morbid or massive obesity (Table 15).

The main characteristics of the 4 patients included in the supplemental cohort were as follows: 3 patients were male, the median age was 16.5 years (range, 8 to 23 years), including 1 patient younger than 12 years, and the mean baseline BMI was 52.06 kg/m^2 corresponding to class III, morbid or massive obesity (55).

Table 15 Patient characteristics on inclusion in Study RM-493-015 (SAS)(55)

	Pivotal cohort (N=11)	Supplemental cohort (N=4)	Total (N=15)
Age at inclusion (years)			
n	11	4	15
Average (standard deviation)	23.7 (8.39)	16.00 (6.78)	21.67 (8.52)
Median	23.0	16.50	23.00
Q1, Q3	15, 31	10.50, 21.50	13.00, 25.00
Min, Max	13, 37	8.0, 23.0	8.0, 37.0
Age group, n (%)			
<12 years old	0	1 (25.0)	1 (6.7)
≥12 years	11 (100.0)	3 (75.0)	14 (93.3)
Gender, n (%)			
Male	3 (27.3)	3 (75.0)	6 (40.0)
Woman	8 (72.7)	1 (25.0)	9 (60.0)
Ethnicity, n (%)			
Caucasian	10 (90.9)	2 (50.0)	12 (80.0)
Other	1 (9.1)	2 (50.0)	3 (20.0)
South Asia	1 (9.1)	0	1 (6.7)
Unknown	0	2 (50.0)	2 (13.3)
Ethnicity, n (%)			
Non-Hispanic and non-Latin	11 (100.0)	2 (50.0)	13 (86.7)
Unknown	0	2 (50.0)	2 (13.3)
Country, n (%)			
United Kingdom	1 (9.1)	0	1 (6.7)
France	4 (36.4)	2 (50.0)	6 (40.0)
Germany	3 (27.3)	1 (25.0)	4 (26.7)
Netherlands	3 (27.3)	0	3 (20.0)
Canada	0	1 (25.0)	1 (6.7)
Weight			
n	11	4	15
Average (standard deviation)	133.265 (26.0200)	130.26 (70.25)	132.46 (39.28)
Median	132.300	133.92	132.30
Q1, Q3	115.47, 153.40	76.56, 183.97	108.57, 159.27
Min, Max	89.37, 170.40	44.6, 208.7	44.6, 208.7
Size (cm)			
n	11	4	15
Average (standard deviation)	166.7 (7.42)	153.00 (19.82)	163.07 (12.76)
Median	166.0	156.50	166.00
Q1, Q3	159, 171	139.50, 166.50	158.00, 171.00
Min, Max	157, 180	126.0, 173.0	126.0, 180.0
BMI (kg/m^2)			
n	11	4	15
Average (standard deviation)	48.17 (10.447)	52.06 (20.30)	49.21 (13.02)
Median	46.63	55.22	46.63
Q1, Q3	38.5, 60.2	35.24, 68.88	38.52, 61.84

	Pivotal cohort (N=11)	Supplemental cohort (N=4)	Total (N=15)
Min, Max	35.8, 64.6	28.1, 69.7	28.1, 69.7
Waist size (cm)			
n	11	4	15
Average (standard deviation)	129.45 (18.414)	125.83 (39.73)	128.49 (24.15)
Median	133.00	124.75	129.50
Q1, Q3	112.0, 149.0	99.25, 152.40	112.00, 149.00
Min, Max	104.0, 154.0	78.5, 175.3	78.5, 175.3

Study RM-493-022

The data presented in Table 16 are those available at the date of database freeze (cut-off) in the initial report (09 May 2019) and concern only the 7 pivotal patients with POMC/PCSK1 mutations. The characteristics of the POMC patients and the PCSK1 patient, included in the initial report rider were similar to those of the POMC pivotal patients.

Table 16 Patient characteristics on inclusion in Study RM-493-022 (56)

	POMC/PCSK1 (N=7)
Age at inclusion (years)	
Average (standard deviation)	18.1 (4.10)
95% CI	14.4, 21.9
Median	17.0
Min, Max	14, 25
Country of investigation site, n (%)	
Germany	7 (100.0)
Gender, n (%)	
Male	4 (57.1)
Woman	3 (42.9)
Ethnicity, n (%)	
Caucasian	6 (85.7)
Other	1 (14.3)
Ethnicity, n (%)	
Non-Hispanic and non-Latin	7 (100.0)
Weight (kg) at study entry index	
Average (standard deviation)	129.59 (27.553)
95% CI	104.10, 155.07
Median	115.20
Min, Max	106.3, 186.7

	POMC/PCSK1 (N=7)
Weight (kg) at inclusion in the extension study	
Average (standard deviation)	91.56 (17.895)
95% CI	75.01, 108.11
Median	85.50
Min, Max	73.9, 121.9
Height (cm) at inclusion in the index study	
Average (standard deviation)	174.71 (11.926)
95% CI	163.68, 185.74
Median	173.00
Min, Max	158.0, 195.0
Height (cm) at inclusion in the extension study	
Average (standard deviation)	176.79 (10.700)
95% CI	166.89, 186.68
Median	173.00
Min, Max	164.5, 195.0
BMI (kg/m^2) at study inclusion index	
Average (standard deviation)	42.29 (5.913)
95% CI	36.82, 47.75
Median	42.60
Min, Max	33.8, 49.9
BMI (kg/m^2) at inclusion in the extension study	
Average (standard deviation)	29.60 (7.468)
95% CI	22.69, 36.51
Median	28.30
Min, Max	22.3, 45,0

Patient baseline characteristics

The mean age of patients enrolled was generally in the late teens to early 20s. Generally, there were similar proportions of male and female patients in setmelanotide trials, apart from study RM-493-015 which had a higher proportion of females. The race of study patients was most-commonly White.

Most patients enrolled into setmelanotide clinical studies were located at study sites in Germany. One patient from study RM-493-015 was located in the United Kingdom (Table 17).

Table 17 Study site location for patients enrolled in setmelanotide clinical trials

Location	RM-493-012 (55)	RM-493-015(55)	RM-493-022(56)
Germany	7	4	7[1]
France	2	6	0
Netherlands	0	3	0
Belgium	2	0	0
United Kingdom	0	1	0
Spain	2	0	0
USA	1	0	0
Canada	1	1	0

[1]The location of 2 of the POMC/PCSK1 patients and the 6 LEPR patients is unknown.

The median BMI for the study population was slightly higher for Study RM-493-015 (Table 18) reflecting the more severe nature of LEPR deficiency obesity.

Table 18 Median baseline BMI for patients enrolled in setmelanotide clinical trials

Location	RM-493-012(55)	RM-493-015(55)	RM-493-022(56)
Pivotal cohort	40.41 kg/m^2	46.63 kg/m^2	[redacted]
All patients	[redacted]	[redacted]	
Index study baseline – POMC patients	[redacted]	[redacted]	[redacted]
Extension study baseline – POMC patients	[redacted]	[redacted]	[redacted]
Index study baseline – LEPR patients	[redacted]	[redacted]	[redacted]
Extension study baseline – LEPR patients[1]	[redacted]	[redacted]	[redacted]

[1] The mean weight on inclusion into the index study was 125.43 kg and was 110.22 kg after approximately 52 weeks in the index study. Mean weight at inclusion in the extension study was 121.87 kg. [redacted] patients with LEPR mutations experienced interruption of setmelanotide therapy of approximately [redacted] after completion of the index study and prior to inclusion in the extension study. This delay in inclusion into the extension study had a marked effect on the mean baseline weight at inclusion in the extension study, as patients had [redacted] weight during the intervening period without setmelanotide treatment.

Delivery of the intervention

Patients in Studies RM-493-012 and RM-493-015 started treatment with a dose-finding phase, during which the setmelanotide dose was increased every 1 or 2 weeks; the individual patient's therapeutic dose was identified based on gradual weight loss and reduction in hunger score. After identification of the therapeutic dose, the patient continued at this dose level for the rest of the study (55).

As patients in Study RM-493-022 had already undergone dose-finding in their initial study, they were maintained on their individual therapeutic dose but the dose could be adjusted to optimise safety/tolerability or efficacy (56).

Setmelanotide was administered as a daily subcutaneous injection by the patient/caregiver for all studies. On clinic days the dose was administered at the study site, with other doses administered by the patient/caregiver at home.

Methodological differences

All studies presented in this document were open label. However, the two pivotal studies (RM-493-012 and RM-493-015) included a 4-week, blinded period to assess the effect of short-term withdrawal of setmelanotide dosing (55).

9.4.4 Subgroup analyses

9.4.4.1 ***Published studies***

The Phase 3 trials (RM-493-012 and RM-493-015) evaluated efficacy outcomes in the designated use set (patients who achieved ≥5 kg weight loss during the 12-week open-label treatment phase or ≥5% for paediatric participants if baseline bodyweight was <100 kg). Clinical biomarkers were analysed for the safety analysis set (55).

9.4.4.2 ***Unpublished data***

Adult and paediatric subgroups were to be assessed for setmelanotide clinical trials. However, very small numbers of patients aged <12 years participated in the trials and so assessment of setmelanotide efficacy in paediatric patients was not possible.

The Study RM-493-022 report dated 10 March 2020 only presents data for POMC/PCKS1 deficiency patients (56). It is planned that subgroup analyses will be conducted in a subsequent report when ≥2 patients with each genetic disorder have completed at least 6 months of treatment in the extension study.

9.4.5 Numbers of patients eligible to enter the studies

9.4.5.1 ***Published data***

Given the rare nature of genetic defects associated with this type of obesity/hyperphagia, patients were identified via mutation databases and/or obesity registries that study investigators were able to access. The investigator-initiated, Phase 2 study (RM-493-011) reported data on 2 patients with POMC mutations and 3 patients with LEPR mutations (27, 54).

The two single-arm, Phase 3 trials reported data on 10 patients with POMC and 11 patients with LEPR mutations. Patient flow through the trials is summarised in Figure 7.

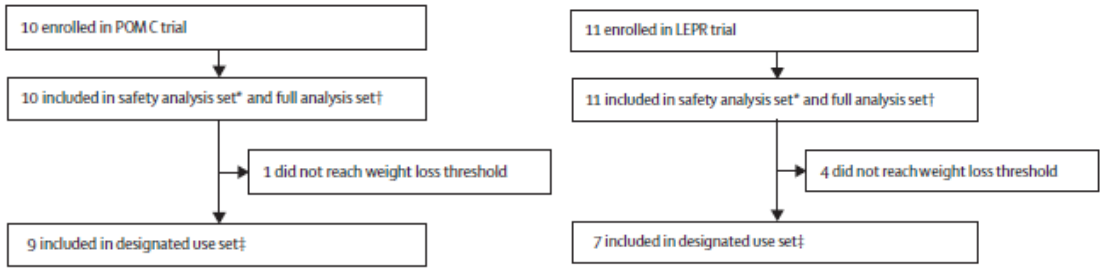


Figure 7 Patient flow diagram through Phase 3 studies

†Received at least one dose of study medication and had a baseline assessment.
‡Participants in the full analysis set who demonstrated ≥5 kg weight loss (or ≥5% for paediatric participants if baseline bodyweight was <100 kg) over the 12-week open-label treatment phase and subsequently proceeded into the placebo-controlled withdrawal sequence.

9.4.5.2 *Unpublished data*

The flow of patients into and through the setmelanotide clinical studies is presented in Table 19 and Table 20. The pivotal studies RM-493-012 and RM-493-015 included two patient cohorts: a pivotal cohort and a supplemental cohort (the latter was formed after the pivotal cohort and included patients who had not completed one year of treatment by the baseline data cut-off date of 09 July 2019). The primary efficacy analysis was based on patients in the pivotal cohort (56).

Three populations provided data for analysis:

- **Full analysis set (FAS)**: patients who received at least one dose of setmelanotide and were evaluated at inclusion.
- **Designated use set (DUS)**: patients who have demonstrated a weight loss equivalent to 5 kg (or 5% if body weight at inclusion <100 kg) over the 12-week open-label treatment period and who have subsequently completed the double-blind, placebo-controlled washout period
- **Safety analysis set (SAS)**: patients who received at least one dose of study drug and with at least one post-administration safety evaluation.

Study RM-493-012

A total of 15 patients were included in Study RM-493-012: 10 patients in the pivotal cohort and 5 patients in the supplemental cohort (55).

The pivotal cohort included 9 patients with POMC biallelic mutations and 1 patient with a PCSK1 biallelic mutation. Of the 10 patients in the pivotal cohort, 9 completed the study and 1 patient discontinued the study due to lack of treatment efficacy (weight loss of 2.7 kg at the end of 8 weeks of open-label treatment, below the established threshold of 5 kg or 5% if body weight at baseline <100 kg, at the end of the 10-week open-label treatment period).

The supplemental cohort included 4 patients with POMC biallelic mutations and 1 patient with a PCSK1 biallelic mutation. Three patients in this cohort completed the study and 2 were withdrawn from the study: one additional patient left the study during the titration phase due to a protocol violation (lack of a POMC/PCSK1 biallelic mutation) and one was considered "lost to follow-up."

Table 19 Disposition of patients in study RM-493-012 (55)

	Pivotal cohort (N=10)	**Supplemental cohort (N=5)**	**Total (N=15)**
Patient status, n (%)			
Screened	10 (100.0)	5 (100.0)	15 (100.0)
Included	10 (100.0)	5 (100.0)	15 (100.0)
Treated	10 (100.0)	5 (100.0)	15 (100.0)
Study population, n (%)			
Designated use set (DUS)	9 (90.0)	4 (80.0)	13 (86.7)
Full analysis set (FAS)	10 (100.0)	4 (80.0)	14 (93.3)
Safety analysis set (SAS)	10 (100.0)	5 (100.0)	15 (100.0)
Study status, n (%)			
Completed the study	9 (90.0)	3 (60.0)	12 (80.0)
Removed from the study	1 (10.0)	2 (40.0)	3 (20.0)
- Lost to view	0	1 (20.0)	1 (6.7)
- Violation of the protocol	0	1 (20.0)	1 (6.7)
- Lack of effectiveness (weight loss <5 kg)	1 (10.0)	0	1 (6.7)

Study RM-493-015

A total of 15 patients were included in Study: RM-493-015 11 patients in the pivotal cohort and 4 patients in the supplemental cohort (55)

The pivotal cohort included 11 patients with LEPR gene mutations. Of the 11 patients in the pivotal cohort, 9 completed the study and 2 discontinued the study: 1 patient died due to injuries in a car accident considered by the investigator to be an unrelated event to the treatment; the other patient due to a grade 1 eosinophilia, considered by the investigator to be probably related to the treatment (55).

All 4 patients in the supplemental cohort completed the study.

Table 20 Disposition of patients in study RM-493-015 (55)

	Pivotal cohort (N=11)	Supplemental cohort (N=4)	Total (N=15)
Patient status, n (%)			
Included	11 (100.0)	4 (100.0)	15 (100.0)
Treated	11 (100.0)	4 (100.0)	15 (100.0)
Study population, n (%)			
Designated use set (DUS)	7 (63.6)	3 (75.0)	10 (66.7)
Full analysis set (FAS)	11 (100.0)	4 (100.0)	15 (100.0)
Safety analysis set (SAS)	11 (100.0)	4 (100.0)	15 (100.0)
Study status, n (%)			
Completed the study	9 (81.8)	4 (100.0)	13 (86.7)
Removed from the study	2 (18.2)	0	2 (13.3)
- Adverse event	1 (9.1)	0	1 (6.7)
- Deaths	1 (9.1)	0	1 (6.7)

RM-493-022

A total of 15 patients were included in the study at the time of the baseline freeze (cuttoff) of the original report rider data (9 POMC/PCSK1 patients and 6 LEPR patients)(56):

- Nine patients with POMC/PCSK1 gene mutations from index study RM-493-012 (8 patients with a POMC biallelic mutation and 1 patient with a PCSK1 biallelic mutation);
- Six patients with LEPR gene mutations from the index study RM-493-015, all of whom were included in the amendment to the original report.

Five of the 9 POMC/PCSK1 patients (55.6%) completed approximately 89 weeks of treatment in the extension study. One patient was withdrawn from the study before completing 37 weeks of treatment.

The 6 LEPR patients (100%) have completed 25 weeks of treatment. The total duration of exposure to setmelanotide therapy in these patients (since inclusion in the index study) ranges from approximately 1.5 to 3 years, as of the baseline freeze date (cut-off) in the original report rider (30 April 2020).

The data presented in Table 21 are those available at the cut-off date of the initial report (09 May 2019) and concern only the 7 pivotal patients with

POMC/PCSK1 mutations. No patients with LEPR mutations had been included and no discontinuations from the study at this cut-off date had been recorded.

Table 21 Disposition of patients in study RM-493-022(56)

	POMC/PCSK1 (N=7)
Patient status, n (%)	
Included in the extension study	7 (100.0)
Addressed in the extension study	7 (100.0)
Total follow-up time (days): from inclusion in index study (N)	7
Average (standard deviation)	707.9 (104.33)
95% CI	611.4, 804.3
Median	724.0
Min, Max	527, 815
Total follow-up time (days): from inclusion in extension study (N)	7
Average (standard deviation)	248.4 (76.92)
95% CI	177.3, 319.6
Median	277.0
Min, Max	114, 311
Extension visit completed, n (%)	
Week 1	7 (100.0)
Week 13	7 (100.0)
Week 25	5 (71.4)
Week 37	5 (71.4)
Stopping treatment	0
Output of the study	0

The data presented in Table 22 are those available at the date of database freeze (cut-off) under the original report rider (30 April 2020).

Table 22 Disposition of patients in study RM-493-022, rider data(56)

	POMC/PCSK1 (N=9)	LEPR (N=6)
Patient status, n (%)		
Included in the extension study	9 (100.0)	6 (100.0)
Extension visit completed, n (%)		
Week 1	9 (100.0)	6 (100.0)
Week 13	9 (100.0)	6 (100.0)
Week 25	9 (100.0)	6 (100.0)
Week 37	8 (88.9)	0
Week 53	7 (77.8)	0
Week 65	7 (77.8)	0
Week 77	6 (66.7)	0
Week 89	5 (55.6)	0
Discontinuation of treatment	1 (11.1)	0
Output of the study	1 (11.1)	0

9.4.6 Details of and the rationale for patients who were lost to follow-up or withdrew from the studies

9.4.6.1 *Published studies*

Two patients discontinued Study RM-493-015, 1 patient died due to injuries sustained as a passenger in a car accident and 1 patient discontinued due to mild eosinophilia (55).

9.4.6.2 *Unpublished studies*

Three patients discontinued Study RM-493-012 (55): 1 patient for lack of efficacy, one following a protocol violation, and the other was lost to follow up. Two patients discontinued Study RM-493-015, 1 patient died due to injuries sustained as a passenger in a car accident after participating in the study for approximately 36 weeks; the event was considered unrelated to study drug and the primary end point was imputed(55). The other patient discontinued due to Grade 1 eosinophilia, which was considered by the Investigator to probably be related to study drug. One patient in Study RM-493-011 discontinued due to a protocol violation(27, 54). No patient in Study RM-493-022 was reported as discontinuing(56).

9.5 Critical appraisal of relevant studies

9.5.1 Quality assessment of studies

9.5.1.1 *Published studies*

Studies were assessed using the modified Critical Appraisal Skills Programme tool, as recommended by NICE for the appraisal of observational evidence in HST submissions. Though the three studies were single-arm trials and not observational studies, this tool was deemed most appropriate for quality assessment given that they did not include a comparator and enrolled small numbers of patients. Critical appraisal of published studies is presented in Table 23.

Table 23 Critical appraisal of published studies

Study Question	RM-493-012 and RM-493-015	RM-493-011	
	Clement, 2020(55)	Kühnen, 2016(54)	Clément, 2018(27)
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
Was exposure accurately measured to minimise bias?	Yes	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes
Did the authors identify all important confounding factors?	Not clear	Not clear	Not clear
Did the authors take account of confounding factors in the design and/or analysis?	No	No	No
Was follow up of patients complete?	Yes	Yes	Yes
Are the results precise (e.g. in terms of CI and p-values)?	Yes	Not applicable	Not applicable

The two Phase 3 setmelanotide trials (RM-493-012 and RM-493-015(55)) recruited eligible patients from available databases and registries. The Phase 2 setmelanotide study (RM-493-011(27, 54)) was an investigator-initiated case series that opportunistically enrolled patients with obesity caused by LEPR and POMC defects. Although there were some concerns regarding a risk of bias due to patient recruitment in the Phase 2 setmelanotide trial, given

the ultra-rare nature of the disease and that opportunistic sampling was the only feasible method for identifying patients, this approach was deemed appropriate.

Setmelanotide studies were single-arm trials rather than true observational studies hence, resulting in no bias due to exposure; similarly, outcomes were measured appropriately by study investigators thereby limiting the risk of bias. However, none of the included studies considered the potential impact of confounding factors on study outcome.

Neither of the Phase 3 studies explicitly stated whether any patients were lost to follow-up; however, the safety analysis and the full analyses set evaluated all patients enrolled in the study at 52 weeks, suggesting that all patients were evaluated at the final outcome assessment. In the Phase 2 case series, patient outcomes were reported at various timepoints depending on the duration of follow-up, presenting no opportunity for bias due to incomplete follow-up.

The Phase 3 studies quantified the accuracy of the treatment effects reporting confidence intervals and p-values. Efficacy outcomes related to obesity markers (i.e., bodyweight, waist circumference, body composition and BMI) were statistically significant with narrow CIs indicating precise estimates.

9.5.1.2 *Unpublished studies*

Critical appraisal of the two pivotal studies is presented in Table 24, with consideration of the long-term extension study presented in Table 25.

Table 24 Critical appraisal of Studies RM-493-012 and RM-493-015(55)

Study question	Response	How is the question addressed in the study?
Was randomisation carried out appropriately?	NA	This was a non-randomised study, with all patients treated with setmelanotide and with placebo (during the double-blind withdrawal period).
Was concealment of treatment allocation adequate?	Yes	Placebo comprised setmelanotide vehicle for subcutaneous injection. Placebo packaging was matched to that of setmelanotide to ensure blinded treatment.
Were the groups similar at the	NA	All patients were assigned to setmelanotide treatment except during the double-blinded

outset of the study in terms of prognostic factors?		withdrawal period; this approach meant that each patient served as their own placebo-control.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Blinding was established so that all patients and study-related staff remained blinded to the timing of study drug/placebo dosing during the 8-week withdrawal period for each patient. No data from the 8-week double-blind placebo-controlled withdrawal period (except for safety reasons) were to be unblinded until the study had completed, all data were cleaned, and the database was locked.
Were there any unexpected imbalances in drop-outs between groups?	NA	All patients were assigned to setmelanotide treatment except during the double-blinded withdrawal period.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The main outcome measures are presented in the body of the clinical study report, with other assessments detailed in the associated Tables and Listings.
Did analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary endpoint was assessed using the FAS. The FAS (or modified intention-to-treat population) provided data on the effect of setmelanotide for all patients who started treatment and had at least a baseline assessment, regardless of whether they met the threshold for continuing into the longer-term study (following individualised dose titration) and the 12-week therapeutic response period on the personalised dose. This population included patients who did not complete the study for any reason. The method for handling missing primary endpoint data at approximately 1 year first examined the reason for missingness. If unrelated to treatment, the endpoint was either extrapolated using a linear model based on existing data or imputed using the longitudinal mixed model. If the reason for missingness was directly related to treatment (lack of efficacy or an adverse event), weight change at approximately 1 year was conservatively

		imputed as 0 kg. Likewise, hunger change at approximately 1 year was imputed as 0. Sensitivity analyses used the following methods, regardless of the reason for missing data: • Weight loss/hunger trends were extrapolated to determine the weight at 1 year; a linear model was fit to individual patient data. • For categorical endpoints, all patients not ongoing on test treatment and missing data at 1 year were considered failures. Ongoing patients had weight/hunger imputed. • The last available observation was carried forward as the weight/hunger at approximately 1 year.

Table 25 Critical appraisal of Study RM-493-022(56)

Study question	Response	How is the question addressed in the study?
Was randomisation carried out appropriately?	NA	This was a non-randomised study, with all patients treated with setmelanotide.
Was concealment of treatment allocation adequate?	NA	This was an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors?	NA	All patients were assigned to setmelanotide treatment.
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA	All patients were assigned to setmelanotide treatment.
Were there any unexpected imbalances in drop-outs between groups?	NA	All patients were assigned to setmelanotide treatment.
Is there any evidence to suggest that the authors measured more	Yes	Samples were collected to identify biomarkers predictive of a setmelanotide response (to support an exploratory objective). At the time of writing the clinical study report, these samples had not been analysed.

outcomes than they reported?		
Did analysis include an intention-to-treat analysis?	No	Efficacy analyses were conducted based on pooling with data from the previous trial and based on genetic defect.

9.6 Results of relevant studies

9.6.1 Results for relevant outcome measures for each study

9.6.1.1 *Published studies*

Clément, 2020(55)

Results showing the efficacy of setmelanotide for the treatment of hyperphagia and obesity in patients with POMC or LEPR deficiency were published by Clément et al.**Error! Bookmark not defined.**in the *Lancet Diabetes & Endocrinology* in 2020. The results are from the Phase 3 studies (RM-493-012 and RM-493-015).

This review looks in detail at the parameters analysed by the different studies previously described (variation in hunger score and weight, changes in waist circumference and BMI, etc.). An analysis was carried out concerning the evolution of anthropometric, cardiovascular and metabolic parameters, the results of which are presented in Table 26.

Table 26 Variation in anthropometric, cardiovascular and metabolic parameters reported by Clément et al. 2020(55)

	POMC patients			LEPR patients		
	At inclusion (n=10)	**At about 1 year of treatment (n=10)**	**Variation from inclusion (n=10)**	**At inclusion (n=11)**	**At about 1 year of treatment (n=9)**	**Variation from inclusion (n=9)**
Weight, kg (DUS)	115.0 (37.8)	83.1 (21.4)	-25.6% (9.9); (90% CI -28.8, -22.0); p<0.0001	131.7 (32.6)	115.0 (29.6)	-12.5% (8.9); (90% CI -16.1, -8.8); p<0.0001
Waist circumference, cm (DUS)	118.9 (17.6)	100.5 (12.4)	-14.9% (7.6); (90% CI -18.4, -11.4); p<0.0001	127.3 (22.5)	114.4 (20.0)	-7.2% (5.0); (90% CI -9.9, -4.0); p=0.0002
Body composition, kg (DUS)						
Non-bone lean mass	57.8 (19.3)	46.6 (10.3)	-10.7% (8.2); (90% CI -14.4, -4.7); p=0.0028	58.5 (9.5)	52.2 (8.5)	-7.4% (5.1); (90% CI -9.2, -4.6); p=0.0004
Total fat mass	55.3 (21.1)	30.3 (11.3)	-38.6% (15.4); (90% CI -50.2, -31.9); p<0.0001	69.3 (24.6)	53.6 (25.1)	-15.0% (14.6); (90% CI -24.8, -6.3); p=0.0086
Cardiovascular parameters						
Heart rate, beats per minute	81.0 (12.1)	75.4 (7.2)	-5.8% (11.4); (90% CI -12.5, 0.8); p=0.14	79.5 (12.6)	77.9 (16.5)	-1.3% (15.5); (90% CI -10.9, 8.3); p=0.80
Diastolic blood pressure, mmHg	73.1 (10.8)	71.5 (9.2)	-1.8% (6.3); (90% CI -5.4, 1.8); p=0.38	67.7 (5.8)	66.5 (8.6)	-1.6% (13.0); (90% CI -9.7, 6.5); p=0.73
Systolic blood pressure, mmHg	111.6 (7.8)	109.8 (6.1)	-1.4% (5.1); (90% CI -4.3, 1.6); p=0.42	121.7 (8.8)	115.1 (14.6)	-3.8% (9.9); (90% CI -9.9, 2.4); p=0.29

	POMC patients			LEPR patients		
	At inclusion (n=10)	**At about 1 year of treatment (n=10)**	**Variation from inclusion (n=10)**	**At inclusion (n=11)**	**At about 1 year of treatment (n=9)**	**Variation from inclusion (n=9)**
Carbohydrate metabolism						
Fasting blood glucose, mg/dL	135.8 (107.7)	107.0 (85.5)	-17.2% (18.8); (90% CI -28.1, -6.3); p=0.018	106.1 (49.2)	108.9 (55.4)	-0.7% (7.0); (90% CI -5.0, 3.7); p=0.78
HbA1c %.	6.1% (1.8)	5.8% (1.9)	-4.0% (10.5); (90% CI -10.1, 2.1); p=0.26	5.7% (0.8)	5.5% (0.7)	-4.9% (7.8); (90% CI -12.3, 2.6); p=0.24
HbA1c, mmol/mol	43.5 (20.5)	39.1 (23.6)	-	54.8 (40.9)	53.8 (38.8)	-
Insulin during oral glucose loading, nmol/L	136.0 (104.6)	78.8 (104.1)	-	134.9 (104.3)	129.5 (40.9)	-
Fat, mg/dL						
HDL	40.4 (17.7)	52.9 (14.1)	45.0% (43.8); (90% CI 19.6, 70.3); p=0.010	41.9 (14.4)	49.2 (16.2)	19.6% (24.0); (90% CI 4.8, 34.5); p=0.040
LDL	88.7 (25.9)	80.6 (28.2)	-7.6% (23.1); (90% CI -21.1, 5.8); p=0.32	105.8 (24.8)	93.3 (22.1)	-10.0% (12.1); (90% CI -17.5, -2.5); p=0.038
Triglycerides	178.4 (158.3)	78.9 (24.8)	-36.6% (30.4); (90% CI -54.2, -19.0); p=0.0041	112.3 (46.0)	96.5 (30.2)	-7.0% (26.6); (90% CI -23.4, 9.5); p=0.46
ALT, IU/L	35.6 (22.3)	17.2 (6.5)	-	22.2 (8.8)	16.8 (7.6)	-
AST, IU/L	33.1 (16.1)	22.2 (5.4)	-	23.4 (5.4)	19.5 (4.04)	-
Bilirubin, µmol/L	7.6 (2.6)	8.2 (3.9)	-	6.8 (3.7)	8.0 (7.4)	-
Creatinine, µmol/L	49.7 (12.5)	55.2 (16.2)	-	58.1 (14.8)	56.6 (17.5)	-

In both Phase 3 clinical trials, setmelanotide was associated with significant improvement in HDL cholesterol concentration (45.0% increase, p=0.010 for POMC/PCSK1 patients and 19.6% increase, p=0.040 for LEPR patients).

For POMC/PCSK1 patients, treatment was also associated with a significant decrease in fasting blood glucose (-17.2% decrease, p=0.018) and triglycerides (-36.6%, p=0.0041).

For LEPR patients, treatment resulted in a significant decrease in LDL cholesterol (-10.0% decrease, p=0.038).

Kühnen, 2016(54)

The 2016 publication by Kühnen et al , in The New England Journal of Medicine, ishows the efficacy of setmelanotide on hyperphagia and obesity in 2 patients with POMC deficiency. These 2 patients were initially included in the Phase 2 (RM-493-011), non-randomised, open-label study, whose primary endpoint was to evaluate the effects of setmelanotide on body weight change after 3 months of treatment.

At inclusion, the first patient, a 21-year-old German woman with a compound heterozygous deficiency for the POMC gene and diagnosed at the age of 4 years, had a weight of 155.0 kg for a BMI of 49.8 kg/m^2 (standard deviation: 4.52) and the second patient, a 26-year-old French woman with a homozygous deficiency for the POMC gene, had a weight of 152.8 kg for a BMI of 54.1 kg/m^2 (standard deviation: 4.78)

Both patients had significant hyperphagia, as indicated by a score of 9 on the Likert hunger scale ranging from 0 (no feeling of hunger) to 10 (extreme hunger). Psychological analyses revealed extreme dissatisfaction with their quality of life due to obesity.

Setmelanotide was injected subcutaneously once daily, with an initial dose of 0.25 mg in Patient 1 and 0.5 mg in Patient 2. These initial doses were increased to 1.5 mg.

At doses below 1.0 mg, patient weight loss was moderate, with little change in their sense of hunger. In contrast, both patients reported a substantial reduction in hunger at higher doses of setmelanotide: the Likert hunger score reduced to 5 at a daily dose of 1.0 mg and between 0 and 1 at the 1.5 mg dose.

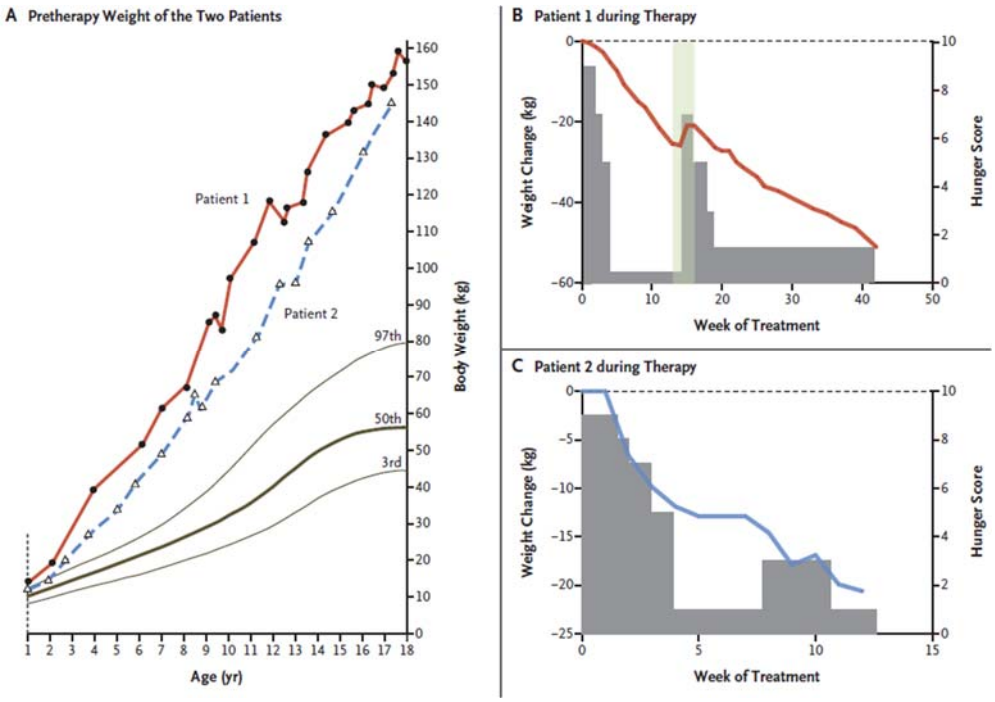
At the 1.5 mg dose, patient 1 had a weight loss of approximately 2 kg per week for a total weight loss of 25.8 kg after the first 13 weeks of treatment (16.6% of her initial body weight with a final body weight of 129.2 kg and a BMI of 41.5 kg/m^2 [3.86]). At the same dose, patient 2 had a weight loss of 20.5 kg at 12 weeks, or 1.7 kg per week (13.4% of initial body weight).

Due to regulatory requirements (toxicology data available for only 3 months), Patient 1 was discontinued from the study after 13 weeks. Shortly thereafter, she reported a marked increase in hunger (Likert hunger score: 7) and regained weight (4.8 kg). Treatment with setmelanotide was resumed (after 3 weeks of discontinuation) and immediately after setmelanotide reintroduction (at a dose of 1.0 mg for 4 weeks and 1.5 mg thereafter) weight loss and a decrease in hunger were observed: weight loss was 1 to 2 kg per week to a total loss of 51.0 kg after 42 weeks of treatment (32.9% of the initial body weight, BMI 33.4 kg/m^2 [2.93]). The main results are detailed in Table 27**Error! Reference source not found.** and Figure 8.

Table 27 Mean change in body weight, BMI, and body composition from baseline reported Kühnen et al. 2016(54)

Change (%) from inclusion	Patient 1			Patient 2	
	Inclusion	Week 13	Week 42	Inclusion	Week 12
Weight, kg	155.0	129.2 (-16.6)	104.0 (-32.9)	152.8	132.3 (-13.4)
BMI, kg/m^2	49.8	41.5 (-8.3)	33.4 (-16.4)	54.1	46.9 (-7.2)
Lean mass, kg	68.7	64.8 (-3.9)	57.5 (-11.2)	59.6	57.0 (-2.6)
Fat mass, kg	88.4	65.2 (-23.2)	47.3 (-41.1)	93.2	75.3 (-17.9)

Figure 8 Weight before setmelanotide therapy and change in weight and hunger score during therapy



Further unpublished data from [redacted] patients enrolled in study RM-493-011 show the [redacted] of weight loss over [redacted] years and [redacted] years respectively.

- Patient [redacted], [redacted] years old at inclusion, went from being [redacted] obese and having an inclusion weight of 152.8 kg to moderate obesity with a weight loss of more than [redacted] kg, to [redacted] kg after about [redacted] years of treatment ([redacted] weeks). The patient has been stabilized for almost [redacted] with a BMI at [redacted]
- Patient [redacted] years old at inclusion, went from [redacted] and an inclusion weight of [redacted] in less than [redacted], with a weight loss of more than [redacted] (lowest weight achieved). The patient has been stabilized with a [redacted] state for almost [redacted] with a weight of [redacted] (Figure 10).

Figure 9 Patient 001-HD_02 long-term data: screening to 230 weeks of treatment (4.4 years)

Figure 10 Patient 001-AB_01 long-term data: screening to 294 weeks of treatment (5.5 years)

9.6.1.2 *Unpublished data for Studies RM-493-012 and RM-493-015(56)*

Statistical considerations

Key analysis populations comprised:

- The FAS (modified intention-to-treat population), defined as all patients who received any study drug and had at least one baseline assessment. The FAS, therefore, included patients who discontinued the study for any reason and those who did not achieve a weight loss response to the individualised treatment dose during the 10-week open-label treatment period.

- The DUS, defined as all patients who received study drug, demonstrated ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over the 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period. The DUS only included patients who achieved the qualifying response necessary for continued treatment after the 10-week open-label treatment period receiving their individualised therapeutic dose; this population was therefore considered to provide the most accurate efficacy evaluation according to setmelanotide's intended use.

Sensitivity analyses were conducted using the FAS, to provide information on the impact of patient discontinuation, either due to lack of efficacy or to lack of tolerability.

The primary endpoint for the pivotal studies was the proportion of patients in the FAS who achieved at least 10% weight loss from baseline (responders) after approximately 1 year of setmelanotide treatment. The null hypothesis was that the proportion was ≤5% and the alternative hypothesis was that the proportion was >5%; the 5% cut-off was based on historical control values. The FDA Draft Guidance of 2007 cites a 5% efficacy benchmark as the target minimum percent decrease for weight-loss agents seeking approval for broad use for management of general common obesity.

It was expected that setmelanotide treatment for 1 year would be associated with a true underlying probability of at least 10% weight loss at 1 year of at least 50%. That assumption yielded at least 94% power to yield a statistically significant (a=0.05 and 0.025, 1-sided) difference from the null hypothesis 5% value for 10 FAS patients. If the true probability of at least 10% weight loss at 1 year was 40%, then power was ~83%. The minimum observed proportion of 10 patients with at least 10% weight loss at 1 year that would yield statistical significance (a=0.05 and 0.025, 1-sided) was 0.3 (3 of 10 patients).

The small number of patients enrolled in this study represent a large proportion of known patients with the disorder; inclusion of such a small population is justified based on the ultra-rare prevalence of the disease

indication. The ability to use extremely rigorous statistical approaches to address multiplicity for many endpoints was limited. Nominal-p-values were, therefore, used to interpret each endpoint separately in this small study where sample size was limited by feasibility. As this approach could increase the probability of potential type-1 error, a step-down procedure was pre-specified to control for type-1 error. For key secondary endpoints, multiplicity was controlled for by stepping down in the following order, if statistical significance was achieved for the primary endpoint:

1. The first key secondary endpoint was change from baseline in body weight at approximately 1-year in the DUS.
2. The second key secondary endpoint was change from baseline in weekly "most hunger in the last 24 hours" hunger scores (on a 0 to 10 scale of 0=not hungry at all, 10=hungriest possible) over approximately 1-year of treatment in DUS patients aged ≥12 years.
3. The third key secondary endpoint was the categorical percent of responder analysis for hunger (using a 25% improvement in hunger threshold) in the FAS at approximately 1-year.

All endpoints are considered relevant to the decision problem. These outcomes were pre-specified in the protocol and all relate directly to assessment of obesity in the patient population in current clinical practice.

Results – Study RM-493-012

Efficacy findings for Study RM-493-012 are presented for primary, secondary and some tertiary endpoints. The primary and key secondary efficacy endpoints were met in this study of patients with POMC-deficiency obesity. Treatment with setmelanotide significantly reduced body weight and hunger scores in POMC-deficiency obese patients, resulting in sustained and clinically meaningful reductions in body weight (55).

Study RM-493-012 primary outcome

The primary endpoint of this study was defined as the proportion of patients in the full analysis set (FAS) of the pivotal cohort who showed at least a 10% reduction in weight at approximately 1 year of treatment from baseline.

Eight of 10 patients (80%) in the pivotal cohort achieved at least a 10% weight loss after approximately 52 weeks of setmelanotide treatment, showing a statistically significant loss of body weight from inclusion (p<0.0001, Table 28).

Table 28 Patients with at least a 10% reduction in weight from baseline in to 52 weeks in Study RM-493-012 (FAS)

Statistics	Pivotal cohort (N=10)	Total (N=14)
n (%)	8 (80.0%)	12 (85.7%)
90% CI	(49.31, 96.32)	(61.46, 97.40)
p-value	<0.0001	<0.0001

The results observed for the supplemental cohort confirmed the results from the pivotal cohort. A total of 85.7% (12 of 14 patients; CI 90% 61.46, 97.40) of included POMC/PCSK1 patients (in both cohorts) showed at least a 10% weight loss at 52 weeks compared with weight on inclusion in the study (p <0.0001).

As of the data cut-off date (09 July 2019), 7 patients in the pivotal cohort (70.0%) had achieved 25% weight loss and 1 patient had achieved up to 35% weight loss, as presented in the Table 29.

Table 29 Patient weight loss from baseline to 52 weeks in Study RM-493-012 (pivotal cohort

Weight reduction threshold at 52 weeks from baseline	Total (N=10)
Patients with a 10% weight reduction	8 (80.0%)
Patients with a 15% weight reduction	8 (80.0%)
Patients with a 20% weight reduction	8 (80.0%)
Patients with a 25% weight reduction	7 (70.0%)
Patients with a 30% weight reduction	3 (30.0%)
Patients with a 35% weight reduction	1 (10.0%)
Patients with a 40% weight reduction	0

RM-493-012 secondary endpoints

The first key secondary endpoint was the mean percent change in body weight from baseline to approximately 1 year of treatment for patients in the DUS. In the 9 patients in the pivotal cohort of the DUS, the mean body weight at inclusion was 114.97 kg. At 52 weeks, there was a significant reduction in

mean body weight of -25.6% from baseline (83.08 kg vs. 114.97 kg, p<0.0001, Table 30).

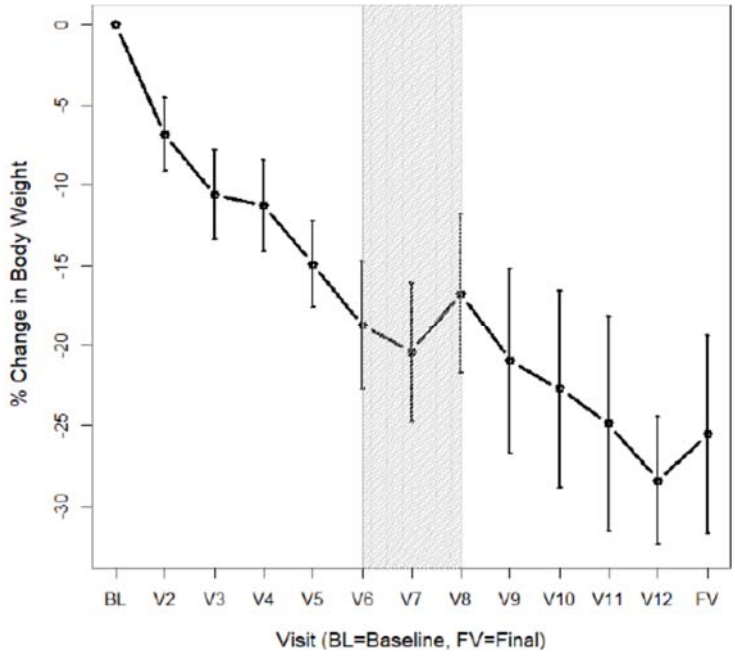
Table 30 Mean change in body weight from inclusion to 52 weeks in Study RM-493-012 (DUS)

	Statistics	Pivotal cohort (N=9)	Total (N=13)
Weight at inclusion (kg)	n	9	13
	Average (SD)	114.974 (37.7740)	108.66 (36.664)
	Median	114.700	114.40
	Q1, Q3	106.30, 130.70	83.67, 130.70
	Min, Max	55.87, 186.73	55.7, 186.7
Weight at 52 weeks (kg)	n	9	13
	Average (SD)	83.076 (21.4250)	79.14 (22.981)
	Median	82.700	82.70
	Q1, Q3	73.90, 95.00	66.9, 95.0
	Min, Max	54.52, 121.80	33.6, 121.8
Change (%) at 52 weeks from inclusion	n	9	13
	Average (SD)	-25.555 (9.8794)	-25.83 (9.721)
	Median	-27.314	-27.31
	Q1, Q3	-30.20, -25.78	-30.67, -20.07
	Min, Max	-35.57, -2.41	-39.6, -2.4
	Least squares (LS) mean	-25.39	-25.73
	90% CI	(-28.80, -21.98)	(-28.49, -22.98)
	p-value	<0.0001	<0.0001

The results observed combined with the supplemental cohort confirm the results of the pivotal cohort: in the 13 patients included (in both cohorts) the mean body weight at inclusion was 108.66 kg. At 52 weeks, there was a significant reduction in mean body weight of -25.83% compared to baseline (79.14 kg vs. 108.66 kg, p<0.0001).

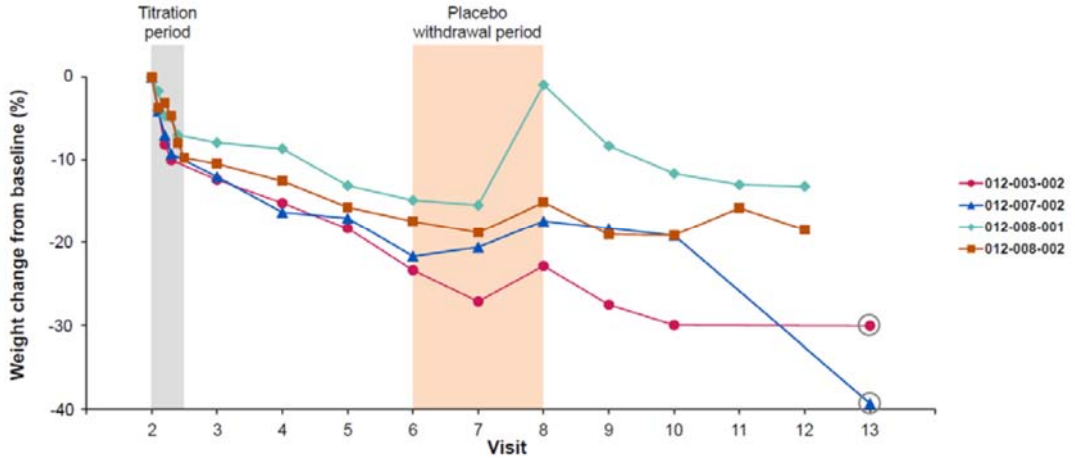
The reduction in weight from baseline for the 9 pivotal patients in the DUS was continuous over the course of the study, as shown in Figure 11; the shaded part of the figure corresponds to the 4-week placebo withdrawal phase.

Figure 11 Mean change in body weight from inclusion to each visit in Study RM 493-012 (pivotal cohort, DUS)



As of the database freeze (cut-off) date for the supplemental data (30 April 2020), the reduction in weight for the 4 patients in the supplemental cohort DUS was broadly continuous over the course of the study, as shown in Figure 12. The coloured part of the figure corresponds to the 4-week placebo treatment period in the withdrawal phase.

Figure 12 Mean change in body weight from inclusion to each visit in Study RM 493-012 (supplemental cohort, DUS)



Average change in hunger score

The second key secondary endpoint of Study RM-493-012 was the mean percent change in the highest hunger score from baseline to approximately 1 year of treatment from baseline in patients at least 12 years of age in the DUS.

The mean score at inclusion of the 7 patients aged ≥12 years in the DUS was 8.1, the mean score at 52 weeks after setmelanotide treatment was 5.8, i.e., a significant mean reduction of -27.1% (p = 0.0005) as presented in Table 31.

Table 31 Mean change in hunger score from inclusion to 52 weeks in Study RM-493-012 (DUS, aged ≥12 years)

	Statistics	Highest hunger score, pivotal cohort (N=7)	Highest hunger score, total (N=8)
Hunger score at inclusion	n	7	7
	Average (SD)	8.1 (0.78)	8.1 (0.78)
	Median	8.0	8.0
	Q1, Q3	7, 9	7.4, 9.0
	Min, Max	7, 9	7, 9
Hunger score at 52 weeks	n	7	8
	Average (SD)	5.8 (2.02)	5.2 (2.52)
	Median	6.0	5.5
	Q1, Q3	4, 8	3.3, 7.4
	Min, Max	3, 8	1, 8
Change from baseline to 52 weeks (%)	n	7	7
	Average (SD)	-27.1 (28.11)	-27.1 (28.11)
	Median	-14.3	-14.3
	Q1, Q3	-55, -3	-54.7, -3.5
	Min, Max	-72, -1	-72, -1
	LS mean	-27.77	-27.77
	90% CI	(-40.58, -14.96)	(-40.58, -14.96)
	p-value	0.0005	0.0005

No inclusion data were available for the 1 patient aged ≥12 years in the supplemental cohort whose hunger score was analysed.

Proportion of patients with ≥25% improvement in hunger score

The third key secondary endpoint Study RM-493-012 was the proportion of patients aged ≥12 years in the FAS who showed ≥25% improvement in highest hunger score at approximately 1 year of treatment compared with inclusion.

This analysis was only performed on responder patients, hence use of the FAS. Four of the 8 patients (50%) in the pivotal cohort FAS achieved ≥25% improvement in hunger score at 52 weeks compared to inclusion with setmelanotide (p=0.0004) as presented in Table 32.

Table 32 Proportion of patients with ≥25% improvement in highest hunger score from inclusion to 52 weeks in study RM-493-012 (FAS, aged ≥12 years

Statistics	Highest hunger score, pivotal cohort (N=8)	Highest hunger score, total (N=9)
Number of patients (%)	4 (50.0%)	4 (50.0%)
90% CI	(19.29, 80.71)	(19.29, 80.71)
p-value	0.0004	0.0004

No inclusion data were available for the 1 patient aged ≥12 years in the supplemental cohort whose hunger score was analysed.

Other secondary and exploratory outcomes

Body mass index

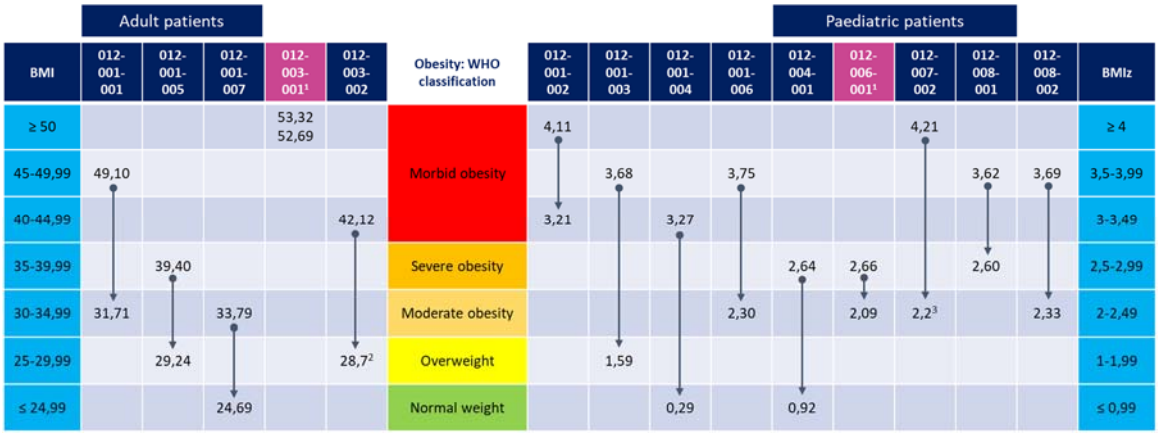
Overweight and obesity are defined on the basis of BMI, obtained by dividing an individual's weight by his or her height squared, which makes it possible to define different stages of severity for the adult population: overweight from 25 kg/m^2, moderate obesity from 30 kg/m^2, severe obesity from 35 kg/m^2, and morbid obesity above 40 kg/m^2.

For a more accurate assessment of BMI in children and adolescents, the BMI Z-score index (or BMIz) provides a numerical indication of deviation from the median for gender and age (35). WHO has established a classification (57) for the population aged 5 to 19 years and defines overweight as BMIz ≥ +1SD and obesity as BMIz ≥ +2SD. Various publications point out that an improvement in BMIz of at least 0.15 to 0.20 points from inclusion represents a minimal clinically important difference (MCID) in patients with obesity (58-61).

An overall mean decrease in BMI of -27.8% (p<0.0001) was observed for the 9 patients in the pivotal cohort (DUS) of Study RM-493-012, transitioning them from severe obesity (mean BMI at baseline of 38.98 kg/m^2) to overweight (mean BMI of 27.76 kg/m^2 at 52 weeks). When the results from the

supplemental cohort were included, there was an overall mean decrease [redacted] for the [redacted] patients (DUS) from [redacted] obesity (mean BMI at inclusion [redacted] kg/m^2) to [redacted] (mean BMI at 52 weeks [redacted]kg/m^2). **Error! Not a valid bookmark self-reference.** presents BMI data by patient.

Figure 13 Analysis of BMI per patient at 52 weeks for POMC/PCSK1patients in Study RM-493-012



Most POMC/PCSK1 patients showed a reduction in BMI and, with the exceptions being patients [redacted] and [redacted]; [redacted] patients also had a reduction of at least [redacted] severity stage at 52 weeks of setmelanotide treatment; [redacted]% of patients ([redacted]) had a reduction of at least [redacted] stages and [redacted]% ([redacted]) a reduction of at least [redacted] stages. Among them, [redacted] had a reduction of [redacted] stages of severity.

It is noteworthy that [redacted]% ([redacted]) of patients had BMI within the normal range ([redacted]) or were [redacted] after 52 weeks of treatment; [redacted] patients (with the exception of patients [redacted] had BMI equivalent to or lower than a [redacted] stage after setmelanotide treatment.

Waist size

The mean waist circumference at inclusion in the 9 patients in the pivotal cohort (DUS) was 118.9 cm and at Week 52 was 100.5 cm, a statistically significant decrease by Week 52 of -14.90% (18.39 cm, p<0.0001, Table 33).

Table 33 Mean change in waist circumference from baseline to 52 weeks in study RM-493-012 (DUS)

	Statistics	Pivotal cohort (N=9)	Total (N=[redacted])
Waist circumference at inclusion (cm)	n	9	[redacted]
	Average (SD)	118.89 (17.574)	[redacted]
	Median	121.00	[redacted]
	Q1, Q3	112.0, 125.0	[redacted]
	Min, Max	86.0, 150.0	[redacted]
Waist circumference at 52 weeks (cm)	n	9	[redacted]
	Average (SD)	100.50 (12.430)	[redacted]
	Median	103.00	[redacted]
	Q1, Q3	95.0, 106.0	[redacted]
	Min, Max	81.0, 121.0	[redacted]
Absolute change from baseline to 52 weeks (cm)	n	9	[redacted]
	Average (SD)	-18.39 (9.867)	[redacted]
	Median	-23.00	[redacted]
	Q1, Q3	-25.0, -10.0	[redacted]
	Min, Max	-29.0, -1.5	[redacted]
	LS mean	-18.31	[redacted]
	90% CI	(-22.35, -14.26)	[redacted]
	p-value	<0.0001	[redacted]

When combined with data from the supplemental cohort: the mean waist circumference in the [redacted] patients at inclusion (DUS) was [redacted] cm and at Week 52 was [redacted] cm, representing a statistically-significant decrease by Week 52 of [redacted] (p<0.0001).

Body weight and hunger score during the withdrawal period

The effects of setmelanotide withdrawal were analysed in terms of changes in body weight and hunger score during the placebo-controlled period compared with those at the time of double-blind reintroduction of setmelanotide. Overall, patients regained weight rapidly and scoring reflected an increase in hunger during the 4-week placebo period. Following reintroduction of setmelanotide, patients generally again showed a significant decrease in hunger and weight.

In the double-blind phase, 8 of 9 patients in the pivotal cohort (DUS) had a mean weight loss of 3.0 kg during the 4 weeks of setmelanotide treatment vs. an increase of 5.5 kg during the 4 weeks of placebo administration, representing a significant 8.5 kg change between the two periods (p=0.0029, Table 34). One patient in the pivotal cohort of the DUS did not complete the placebo-controlled period and was not included in the analysis because of an

error in the administration sequence for placebo and setmelanotide. However, sensitivity analysis was conducted with all 9 patients showed consistent results.

Table 34 Absolute change in body weight during the withdrawal period of study RM-493-012 (DUS)

	Statistics	Pivotal cohort (N=9)	Total (N=[redacted])
Setmelanotide dosing period	n	8	
	Average (SD)	-3.000 (2.5194)	
	Median	-3.400	
	Q1, Q3	-4.88, -0.78	
	Min, Max	-6.40, 0.54	
Placebo dosing period	n	8	
	Average (SD)	5.515 (3.0531)	
	Median	5.100	
	Q1, Q3	3.60 ; 7.35	
	Min, Max	1.53, 10.50	
Difference between the two periods	n	8	
	Average (SD)	8.515 (5.3775)	
	Median	8.500	
	Q1, Q3	4.58, 11.93	
	Min, Max	1.20, 16.90	
	90% CI	(4.91, 12.12)	
	p-value	0.0029	

The data for the pivotal and supplemental cohorts [redacted] these findings: in [redacted] patients there was a mean weight loss of [redacted] during the 4 weeks of setmelanotide treatment vs. an increase of [redacted] during the 4 weeks of placebo dosing, representing a significant difference between periods of [redacted].

The mean hunger score in 6 of 7 patients aged ≥12 years in the pivotal cohort (DUS) was 4.9 during setmelanotide administration and 7.1 during placebo dosing, a difference of 2.2 between periods (p=0.1913, Table 35).

Table 35 Absolute change in highest hunger score during the withdrawal period of Study RM-493-012 (DUS)

	Statistics	Highest hunger score, pivotal cohort (N=7)	Highest hunger score, total (N=[redacted])
Setmelanotide dosing period	n	6	[redacted]
	Average (SD)	4.9 (2.55)	[redacted]
	Median	5.1	[redacted]
	Q1, Q3	3, 7	[redacted]
	Min, Max	1, 7	[redacted]
Placebo dosing period	n	6	[redacted]
	Average (SD)	7.1 (2.07)	[redacted]
	Median	6.9	[redacted]
	Q1, Q3	5, 9	[redacted]
	Min, Max	5, 10	[redacted]
Difference between the two periods	n	6	[redacted]
	Average (SD)	2.2 (3.62)	[redacted]
	Median	2.5	[redacted]
	Q1, Q3	-2, 5	[redacted]
	Min, Max	-2, 7	[redacted]
	90% CI	(-0.75, 5.21)	[redacted]
	p-value	0.1913	[redacted]

When combined with data for the supplemental cohort: mean hunger score for the [redacted] patients aged ≥12 years in the DUS was [redacted] when setmelanotide was administered and [redacted] with placebo dosing, a difference of [redacted] between period [redacted].

Body mass composition

Overall, 75.6% of the body weight loss observed in the pivotal cohort (DUS) was from body fat, with an average loss of 20.3 kg of body fat for an average body mass loss of 26.9 kg (When combined with data for the supplemental cohort: [redacted]% of body weight loss observed was from body fat, with an average loss of [redacted] kg of body fat for an average body mass loss of [redacted] kg. Body mass reduced by [redacted]% while body fat reduced by [redacted]%.

Table 36). Body mass reduced by 23.90% while body fat reduced by 38.64%. It should be noted that there was no loss of bone density and minimal loss of non-bone lean body mass.

When combined with data for the supplemental cohort: [redacted]% of body weight loss observed was from body fat, with an average loss of [redacted] kg of body fat for an average body mass loss of [redacted] kg. Body mass reduced by [redacted]% while body fat reduced by [redacted]%.

Table 36 Change in body mass and fat from baseline to 52 weeks in Study RM-493-012 (DUS)

		Pivotal cohort (n=9)		Total (N=[redacted])	
	Statistics	**Body mass**	**Fat mass**	**Body mass**	**Fat mass**
At inclusion	n	9	9	[redacted]	[redacted]
	Average (SD)	113278.90 (38778.742)	55255.44 (21088.259)	[redacted]	[redacted]
	Median	113300.00	51200.00	[redacted]	[redacted]
	Q1, Q3	103400.0, 127800.0	47700.0, 66200.0	[redacted]	[redacted]
	Min, Max	54620.1, 186200.0	24884.0, 91900.0	[redacted]	[redacted]
At 52 weeks	n	8	8	[redacted]	[redacted]
	Average (SD)	77263.94 (17513.334)	30328.34 (11278.019)	[redacted]	[redacted]
	Median	78250.00	25366.35	[redacted]	[redacted]
	Q1, Q3	64090.8, 90200.0	21697.0, 40050.0	[redacted]	[redacted]
	Min, Max	51830.0, 101200.0	19500.0, 48900.0	[redacted]	[redacted]
Absolute change from baseline to 52 weeks (g)	n	8	8	[redacted]	[redacted]
	Average (SD)	-26899.83 (13355.972)	-20346.54 (9171.241)	[redacted]	[redacted]
	Median	-30850.00	-23000.00	[redacted]	[redacted]
	Q1, Q3	-35900.0, -20980.0	-26550.0, -16160.5	[redacted]	[redacted]
	Min, Max	-39500.0, -238.6	-29500.0, -1851.3	[redacted]	[redacted]
	LS mean	-28732.80	-23371.93	[redacted]	[redacted]
	90% CI	(-31973.05, -25492.55)	(-28861.57, -17882.29)	[redacted]	[redacted]
	p-value	<0.0001	<0.0001	[redacted]	[redacted]
Percent change from baseline to 52 weeks (%)	n	8	8	[redacted]	[redacted]
	Average (SD)	-23.90 (10.203)	-38.64 (15.395)	[redacted]	[redacted]
	Median	-26.53	-37.64	[redacted]	[redacted]
	Q1, Q3	-28.0, -23.5	-48.8, -34.7	[redacted]	[redacted]
	Min, Max	-34.9, -0.4	-59.3, -7.4	[redacted]	[redacted]
	LS mean	-24.47	-41.01	[redacted]	[redacted]
	90% CI	(-28.45, -20.49)	(-50.15, -31.88)	[redacted]	[redacted]
	p-value	<0.0001	<0.0001	[redacted]	[redacted]

Quality of life data for Study RM-493-012

Different quality of life scales were used depending on the patient age:

- For patients under 18 years of age, quality of life was assessed using a self-assessment tool validated for the paediatric population, the PedsQL (Pediatric Quality of Life Inventory) questionnaire (62) and the SF-10 questionnaire, also adapted to the paediatric population and allowing for patient self-assessment and caregiver (parent) report.
- For patients aged 18 years and older, quality of life was assessed using the validated, obesity-specific self-report tool, Impact of Weight on Quality of Life-Lite (IWQOL-Lite) (63) and the Short Form Health Survey (SF-36) to measure patients' functional health and well-being.

The PedsQL questionnaire assesses health-related quality of life in diverse paediatric populations, including healthy children and children with chronic or acute conditions. The 23 test items are grouped into 4 domains: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and academic functioning (5 items).

The IWQoL-Lite questionnaire is a short version of the IWQoL and includes 31 items (compared to 75 in the long version), divided into 5 dimensions: physical mobility, self-image, sexuality, social life and work. Scores are transcribed in a linear fashion on a scale between 0 and 100, summed and divided by the number of items completed; higher scores being associated with better health-related quality of life. Various publications point out that an improvement in the total IWQOL-Lite score of 7 to 12 points from inclusion represents a MCID in patients with obesity (64, 65). The scores presented **Error! Reference source not found.** indicate the total score after cumulating the result of each of the domains) at the database freeze of the (cut-off) of the initial data (09 July 92019).

For the [redacted] patients aged 18 years or older, there was a mean 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],Table 37). The difference of [redacted] points [redacted] is greater than the MCID suggested in the literature (65, 66), underscoring the clinical relevance of improving this score.

relevance of improving this score.

Table 37 Change in total IWQOL-Lite score from inclusion in RM-493-012 for patients aged 18 years or older (pivotal cohort, DUS)

Parameter	Statistics	Total (N=[redacted])
At inclusion	n	
	Average (SD)	
	Median	
	Q1, Q3	
	Min, Max	
At 52 weeks	n	
	Average (SD)	
	Median	
	Q1, Q3	
	Min, Max	
Percent change at 52 weeks from inclusion (%)	n	
	Average (SD)	
	Median	
	Q1, Q3	
	Min, Max	
	LS mean	
	90% CI	
	p-value	

Regarding paediatric patients (a significant mean improvement of [redacted]% was observed in total PedsQL score [redacted] assessed by children and [redacted] assessed by the parents of 2 patients aged 8 and 12 years.

- a significant mean improvement of [redacted]% was observed in total PedsQL score [redacted] assessed by children and [redacted]% [redacted] assessed by the parents of [redacted] patients aged 13 to 18 years.

Table 38**Error! Reference source not found.**):

- a significant mean improvement of [redacted]% was observed in total PedsQL score [redacted] assessed by children and [redacted] assessed by the parents of 2 patients aged 8 and 12 years.

- a significant mean improvement of [redacted]% was observed in total PedsQL score [redacted] assessed by children and [redacted]% [redacted] assessed by the parents of [redacted] patients aged 13 to 18 years.

Table 38 Change in total PedsQL score from inclusion in Study RM-493-012 for the paediatric population (pivotal cohort, DUS)

Parameter	Statistics	Patients 8 to 12		Patients 13 to 18 years	
		Assessed by parent, total (N=[redacted])	Evaluated by patient, total (N=[redacted])	Assessed by parent, total (N=[redacted])	Evaluated by patient, total (N=[redacted])
At inclusion	n	[redacted]	[redacted]	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
At 52 weeks	n	[redacted]	[redacted]	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Percent change from inclusion to 52 weeks (%)	n	[redacted]	[redacted]	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	LS mean	[redacted]	[redacted]	[redacted]	[redacted]
	90% CI	[redacted]	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]	[redacted]

Results – Study RM-493-015

Efficacy findings for Study RM-493-015 are presented for primary, secondary and some tertiary endpoints. Primary and key secondary efficacy endpoints in this study of patients with LEPR-deficiency obesity were met. Treatment with setmelanotide significantly reduced body weight and hunger scores in LEPR-deficiency obese patients, resulting in sustained and clinically-meaningful reductions in body weight and hunger.

RM-493-015 primary outcome

The primary endpoint of this study was defined as the proportion of patients in the FAS for the pivotal cohort who showed at least a 10% reduction in weight at approximately 1 year of treatment from baseline.

Five of the 11 patients (45.5%) in the pivotal cohort achieved a weight loss of at least 10% after approximately 52 weeks of setmelanotide treatment,

showing a statistically significant loss of body weight from inclusion (p<0.0001, Table 39). Among these 5 patients the maximum weight loss was 25%.

Table 39 Patients with at least 10% reduction in weight from baseline to Week 52 in Study RM-493-015 (FAS)

Statistics	Pivotal cohort (N=11)	Total (N=15)
n (%)	5 (45.5%)	8 (53.3%)
90% CI	(19.96, 72.88)	(30.00, 75.63)
p-value	<0.0001	<0.0001

The results observed in the supplemental cohort confirm the results of the pivotal cohort. A total of 53.3% (8 of 15 patients; 90% CI 30.00, 75.63) of LEPR patients included in both cohorts showed at least 10% weight loss at 52 weeks from baseline (p<0.0001).

As of data cut-off date (15 July, 2019) 5 patients in the pivotal cohort (45.5%) had achieved 15% weight loss and 2 patients had achieved up to 20% weight loss. The overall results are presented in Table 40**Error! Reference source not found.**.

Table 40 Weight loss from baseline to 52 weeks in Study RM-493-015 (pivotal cohort)

	Total (N=11)
Patients with a 5% reduction	6 (54.5%)
Patients with a 10% reduction	5 (45.5%)
Patients with a 15% reduction	5 (45.5%)
Patients with a 20% reduction	2 (18.2%)
Patients with a 25% reduction	0
Patients with a 30% reduction	0
Patients with a 35% reduction	0
Patients with a 40% reduction	0

Results of key secondary endpoints

Average change in body weight

The first key secondary endpoint of this study was the mean percent change in body weight from baseline to approximately 1 year of treatment for patients in the DUS. For 7 of 11 patients in the pivotal cohort DUS, mean body weight

at inclusion was 131.7 kg. At 52 weeks, there was a significant reduction in mean body weight of -12.47% (16.7 kg) from baseline (115.0 kg vs 131.7 kg, p<0.0001, Table 41).

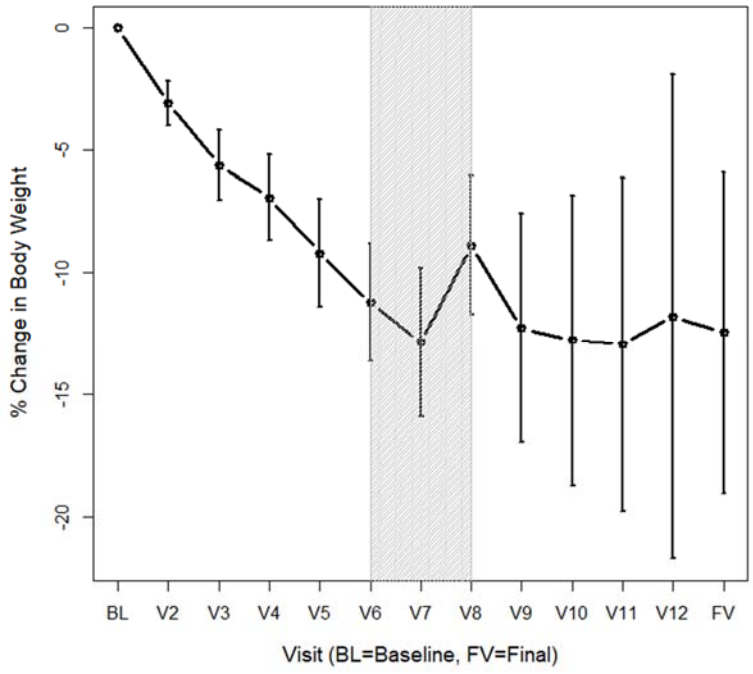
Table 41 Mean change in body weight from inclusion to 52 weeks in Study RM-493-015 (DUS)

	Statistics	Pivotal cohort (N=7)	Total (N=10)
Weight at inclusion (kg)	n	7	10
	Average (SD)	131.738 (32.6134)	139.87 (37.909)
	Median	120.533	136.97
	Q1, Q3	103.43, 169.57	108.57, 169.57
	Min, Max	89.37, 170.40	89.4, 208.7
Weight at 52 weeks (kg)	n	7	10
	Average (SD)	115.001 (29.5991)	122.65 (35.022)
	Median	104.100	123.89
	Q1, Q3	89.45, 143.75	90.87, 146.25
	Min, Max	81.70, 149.92	81.7, 184.3
Change from baseline to 52 weeks (%)	n	7	10
	Average (SD)	-12.467 (8.9185)	-12.34 (7.534)
	Median	-15.281	-13.47
	Q1, Q3	-21.01, -2.27	-16.30, -8.17
	Min, Max	-23.31, 0.09	-23.3, 0.1
	LS mean	-12.47	-12.37
	90% CI	(-16.10, -8.83)	(-15.08, -9.66)
	p-value	<0.0001	<0.0001

When combined with the supplemental cohort data the results confirmed the findings for the pivotal cohort: baseline body weight for the 10 patients in the pivotal and supplemental cohorts was 139.87 kg; by 52-weeks they reached a weight of 122.65 kg, a mean percent change in body weight from inclusion to 52 weeks of -12.34% (p<0.0001).

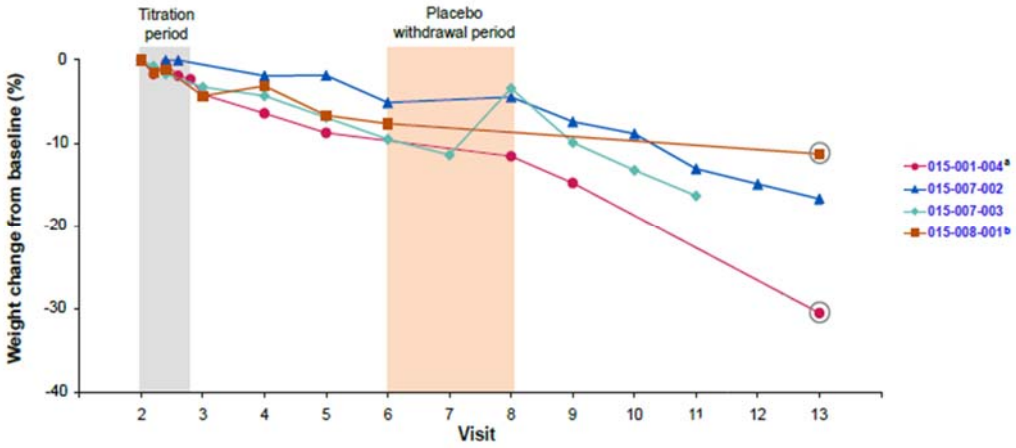
The reduction in weight from baseline for patients in the pivotal cohort was continuous over the course of the study, as shown in Figure 14. The shaded area corresponds to the 4-week placebo treatment period in the withdrawal phase.

Figure 14 Mean change in body weight at each visit from inclusion in Study RM-493-015 (pivotal cohort, DUS)



At data cut-off for supplemental cohort data (30 April 2020), the results from the pivotal cohort were confirmed: Figure 15 shows the mean change in body weight at each visit from baseline for patients in the supplemental cohort. The area corresponds to the 4-week placebo treatment period in the withdrawal phase.

Figure 15 Mean change in body weight at each visit from inclusion in Study RM-493-015 (supplemental cohort, DUS)



Patient 001-004 did not receive placebo
Patient 008-001 withdrew after starting the placebo-controlled withdrawal phase

Average change in hunger score

The second key secondary endpoint was the mean percent change in the highest hunger score from baseline to approximately 1 year of treatment in patients aged ≥ 2 years. The mean score on study inclusion for the 7 patients aged ≥12 years in the pivotal cohort was 7.0 and the mean score after 52 weeks of setmelanotide treatment was 4.1, representing a significant mean reduction of -43.7% (p<0.0001, Table 42).

Table 42 Mean change in hunger score from inclusion to 52 weeks in Study RM-493-015 (DUS, aged ≥12 years)

	Statistics	Highest hunger score, pivotal cohort (N=7)	Highest hunger score, total (N=10)
Hunger score at inclusion	n	7	10
	Average (SD)	7.0 (0.77)	6.9 (1.10)
	Median	7.0	6.9
	Q1, Q3	6, 8	6.3, 8.0
	Min, Max	6, 8	5, 9
Hunger score at 52 weeks	n	7	10
	Average (SD)	4.1 (2.09)	4.0 (2.13)
	Median	3.0	3.2
	Q1, Q3	2, 5	2.3, 5.0
	Min, Max	2, 8	2, 8
Change from inclusion to 52 weeks (%)	n	7	10
	Average (SD)	-43.7 (23.69)	-42.7 (27.49)
	Median	-52.7	-54.4
	Q1, Q3	-64, -29	-64.3, -28.6
	Min, Max	-67, 0	-67, 7
	LS mean	-41.93	-42.69
	90% CI	(-54.76, -29.09)	(-56.35, -29.02)
	p-value	< 0.0001	< 0.0001

When combined with the supplemental cohort the results confirmed those from the pivotal cohort: the hunger score for the 10 patients in the combined cohorts was 6.9 at inclusion and 4.0 at 52 weeks, representing a significant reduction of -42.7% (p<0.0001).

Proportion of patients with ≥25% improvement in hunger score

The third key secondary end point For Study RM-493-015 was the proportion of patients aged ≥12 years in the FAS with a ≥25% improvement in highest hunger score from inclusion to approximately 1 year of treatment.

This analysis was only performed on responding patients and thus was assessed using the FAS. Eight of the 11 patients (72.7%) in the pivotal cohort achieved ≥25% improvement in hunger score from inclusion to 52 weeks (p<0.0001, Table 43).

Table 43 Proportion of patients showing ≥25% improvement in highest hunger score from baseline to 52 weeks in Study RM-493-015 (FAS, aged ≥12 years)

Statistics	Highest hunger score, pivotal cohort (N=11)	Highest hunger score, total (N=14)
n	8 (72.7%)	10 (71.4%)
90% CI	(43.56, 92.12)	(46.00, 89.60)
p-value	<0.0001	<0.0001

When combined with the supplemental cohort results the data were supportive of the findings for the pivotal cohort: 10 of 14 patients (71.4%; CI 90% 46.00, 89.60; p<0.0001) in the combined pivotal and supplemental cohorts aged ≥12 years had an improvement of ≥25% in highest hunger score.

Other secondary, tertiary and exploratory outcomes

Body mass index

An overall mean decrease in BMI of -13.0% (p<0.0001) was observed for the 7 patients in the pivotal cohort (DUS) of study RM-493-015, this transitioned them from massive obesity (mean baseline BMI of 47.5 kg/m^2) to severe obesity (mean BMI at 52 weeks of 38.8 kg/m^2). Figure 16 shows individual patient BMI data after 52 weeks of treatment.

Figure 16 Analysis of individual patient BMI at 52 weeks, LEPR patients

[1] Non-responders for the primary endpoint
[2] After 35 weeks of treatment
[3] After 8 weeks of treatment

The BMIz severity stages (from overweight 1 to 1.99 to obese ≥ 2) are [redacted] the MCID suggested in different publications (0.15 to 0.20 points(54, 59-61), highlighting the clinical relevance of the improved score in terms of changes in the severity of obesity on an individual-patient basis.

[redacted] LEPR patients had a reduction in BMI, [redacted] patients ([redacted]%) had a reduction of at least [redacted] severity stage after 52 weeks of setmelanotide treatment and [redacted] patients ([redacted]%) of at least [redacted] severity stages.

Waist size

The mean waist circumference on inclusion into Study RM-493-015 for the 7 patients of the pivotal cohort (DUS) was 127.3 cm and at Week 52 was 114.4 cm, representing a statistically significant decrease of 7.24% (9.10 cm, p=0.0001, Table 44).

Table 44 Mean change in waist circumference from inclusion to 52 weeks in Study RM-493-015 (DUS)

Parameter	Statistics	Pivotal cohort (N=7)	Total (N=[redacted])
Waist circumference at inclusion (cm)	n	7	[redacted]
	Average (SD)	127.29 (22.455)	[redacted]
	Median	114.00	[redacted]
	Q1, Q3	108.0, 150.0	[redacted]
	Min, Max	104.0, 154.0	[redacted]
Waist circumference at 52 weeks (cm)	n	6	[redacted]
	Average (SD)	114.40 (20.031)	[redacted]
	Median	106.75	[redacted]
	Q1, Q3	102.5, 136.5	[redacted]
	Min, Max	92.0, 141.9	[redacted]
Absolute change from baseline to 52 weeks (cm)	n	6	[redacted]
	Average (SD)	-9.10 (6.361)	[redacted]
	Median	-7.55	[redacted]
	Q1, Q3	-16.0, -4.5	[redacted]
	Min, Max	-17.5, -1.5	[redacted]
	LS mean	-8.84	[redacted]
	90% CI	(-12.45, -5.24)	[redacted]
	p-value	0.0001	[redacted]

When combined with data for the supplemental cohort the results for the pivotal cohort [redacted]: the mean waist circumference at inclusion in the study for the [redacted] patients in the combined cohort was [redacted] and decreased to [redacted] by 52 weeks, representing a statistically significant decrease of [redacted].

Body weight and hunger score during the withdrawal period

The effects of setmelanotide withdrawal were analysed in terms of changes in body weight and hunger score during the placebo-controlled period compared with those at the time of double-blind reintroduction of setmelanotide. Patients gained weight rapidly during the 4-week placebo period and hunger scores indicated an increase in hunger. Following reintroduction of setmelanotide, patients generally showed a significant decrease in hunger and weight.

In the double-blind phase, the 7 patients in the pivotal cohort had a mean weight loss of 2.1 kg during the 4 weeks of setmelanotide treatment vs. an increase of 5.0 kg during the 4 weeks of placebo administration; this represents a significant change between the two periods of 7.0 kg (p=0.0014, Table 45).

Table 45 Absolute change in body weight during the withdrawal period in Study RM-493-015 (DUS)

Period	Statistics	Pivotal Cohort (N=7)	Total (N=[redacted])
Setmelanotide	n	7	[redacted]
	Average (SD)	-2.060 (1.7314)	[redacted]
	Median	-2.167	[redacted]
	Q1, Q3	-3.63, -1.20	[redacted]
	Min, Max	-4.15, 1.05	[redacted]
Placebo	n	7	[redacted]
	Average (SD)	4.974 (2.3010)	[redacted]
	Median	4.067	[redacted]
	Q1, Q3	2.90, 6.50	[redacted]
	Min, Max	2.85, 9.03	[redacted]
Difference between the two periods	n	7	[redacted]
	Average (SD)	7.033 (3.3532)	[redacted]
	Median	7.000	[redacted]
	Q1, Q3	5.63, 9.25	[redacted]
	Min, Max	1.85, 12.67	[redacted]
	90% CI	(4.57, 9.50)	[redacted]
	p-value	0.0014	[redacted]

When combined with the supplemental cohort [redacted] the results supported those for the pivotal cohort: for [redacted] patients in both cohorts there was a mean weight loss of [redacted] during the 4 weeks of setmelanotide treatment vs. an increase of [redacted] during the 4 weeks of placebo administration, representing a significant change between the two periods of [redacted].

The mean hunger score for [redacted] patients aged ≥12 years was [redacted] during setmelanotide administration and [redacted] during the placebo period, a difference of [redacted] between the two periods ([redacted], **Error! Not a valid bookmark self-reference.**).

Table 46 Absolute change in highest hunger score during the withdrawal period in Study RM-493-015 (DUS)

Period	Statistics	Pivotal cohort (N=7)	Total (N=[redacted])
Setmelanotide	n	7	[redacted]
	Average (SD)	3.1 (1.57)	[redacted]
	Median	2.8	[redacted]
	Q1, Q3	2, 4	[redacted]
	Min, Max	2, 6	[redacted]
Placebo	n	6	[redacted]
	Average (SD)	6.4 (2.25)	[redacted]
	Median	5.6	[redacted]
	Q1, Q3	5, 8	[redacted]
	Min, Max	4, 10	[redacted]
Difference between the two periods	n	6	[redacted]
	Average (SD)	3.1 (2.71)	[redacted]
	Median	2.6	[redacted]
	Q1, Q3	1, 5	[redacted]
	Min, Max	0, 7	[redacted]
	90% CI	(0.87, 5.32)	[redacted]
	p-value	0.0380	[redacted]

When combined with the supplemental cohort: [redacted] patients aged ≥12 years had a mean hunger score of [redacted] when setmelanotide was administered and [redacted] with placebo, representing a difference of [redacted] between the two time periods [redacted].

Body mass composition

Overall, 67.3% of the body weight loss observed in LEPR patients was from body fat comprising an average loss of 8.7 kg body fat for an average body mass loss of 12.9 kg. Body mass reduced by 11.05% while body fat reduced by 15.03%. It should be noted that there was no loss of bone density and minimal loss of non-bone lean body mass (Table 47).

Table 47 Change in body mass and fat from inclusion to 52 weeks in Study RM-493-015 (pivotal cohort, DUS)

Parameter	Statistics	Body mass, total (N=[redacted])	Fat mass, total (N=[redacted])
At inclusion	n	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
At 52 weeks	n	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Absolute change from inclusion to 52 weeks (g)	n	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
	LS mean	[redacted]	[redacted]
	90% CI	[redacted]	[redacted]
	p-value	[redacted]	[redacted]
Percent change from inclusion to 52 weeks (%)	n	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
	LS mean	[redacted]	[redacted]
	90% CI	[redacted]	[redacted]
	p-value	[redacted]	[redacted]

Quality of life data for Study RM-493-015

The quality of life of patients in study RM-493-015 was assessed using the same protocol and quality-of-life scales as those used in study RM-493-012 (PedsQL and IWQOL-Lite). At the baseline freeze date (15 July 2019), for the [redacted] patients aged ≥18 years there was an average increase of [redacted] in total IWQOL-Lite score: comprising a score of [redacted] at inclusion increasing to [redacted] at 52 weeks, representing a significant difference of [redacted] points between scores ([redacted], Table 48); this difference is [redacted] than the MCID suggested by various publications, highlighting the clinical relevance of treatment (66).

Table 48 Change in total IWQOL-Lite score from inclusion in RM-493-015 for patients aged ≥18 years (pivotal cohort, DUS)

	Statistics	Total (N=[redacted])
At inclusion	n	[redacted]
	Average (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
At 52 weeks	n	[redacted]
	Average (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Percent change from inclusion to 52 weeks (%)	n	[redacted]
	Average (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
	LS mean	[redacted]
	90% CI	[redacted]
	p-value	[redacted]

As of the date of the baseline freeze (cut-off) of supplemental cohort data (30 April 2020), quality of life data for paediatric LEPR patients were not available.

Table 49 Summary of patient outcomes for Studies RM-493-012 and RM-493-015

		RM-493-012	RM-493-015
Size of study groups	**Treatment**	Setmelanotide N=15 enrolled, FAS=14, DUS=13	Setmelanotide N=15 enrolled, FAS=15, DUS=10
	Control	Placebo (during the 8-week withdrawal period) N=13	Placebo (during the 8-week withdrawal period) N=9
Study duration	**Time unit**	1 year (52 weeks of treatment)	
Outcome	**Name**	Primary endpoint – the proportion of patients with 10% body weight loss from baseline	
	Unit	Number of patients (%)	
Type of analysis	**FAS**	(modified intention-to-treat), N=14	(modified intention-to-treat), N=15
Effect size	**Value**	12 patients (85.7%)	8 patients (53.3%)
	90% CI	61.46, 97.40	30.00, 75.63
Statistical test	**Type**	Exact binomial test at a 1-sided 5% significance level, with corresponding 2-sided 90% CIs calculated using the exact Clopper-Pearson method	
	p value	<0.0001	<0.0001
Other outcome	**Name**	Key secondary endpoint - mean change in body weight from baseline	
	Unit	%	%
Type of analysis	**DUS**	N=13	N=10
Effect size	**Value**	Least square (LS) mean -25.73	LS mean -12.37
	90% CI	-28.49, -22.98	-15.08, -9.66
Statistical test	**Type**	Model-based summary statistics from a longitudinal mixed ANOVA with fixed effect for visit, baseline body weight and random effect for patient	
	p value	<0.0001	<0.0001

		RM-493-012	RM-493-015
Other outcome	**Name**	Key secondary endpoint - change in hunger score from baseline	
	Unit	%	
Type of analysis	**DUS**	patients aged ≥12 years, N=8	patients aged ≥12 years, N=10
Effect size	**Value**	LS mean change in morning hunger -11.08	LS mean change in morning hunger -46.46
	90% CI	-37.78, 15.62	-68.14, -24.77
	p value	0.2447	0.0004
	Value	LS mean change in worst (most) hunger in 24 hours -27.77	LS mean change in worst (most) hunger in 24 hours -42.69
	90% CI	-40.58, -14.96	-56.35, -29.02
	p value	0.0005	<0.0001
	Value	LS mean change in average hunger in 24 hours -33.11	LS mean change in average hunger in 24 hours -47.72
	90% CI	-47.90, -18.31	-60.72, -34.73
	p value	0.0006	<0.0001
Statistical test	**Type**	Model-based summary statistics from a longitudinal mixed ANOVA with fixed effect for week, baseline daily hunger score and random effect for patient	
Other outcome	**Name**	Key secondary endpoint - proportion of patients achieving at least 25% improvement in hunger score from baseline	
	Unit	Number of patients (%)	
Type of analysis	**FAS**	(modified intention-to-treat) patients aged ≥12 years, N=9	(modified intention-to-treat) patients aged ≥12 years, N=14
Effect size	**Value**	5 patients (62.5%) with improvement in morning hunger	9 patients (64.3%) with improvement in morning hunger
	90% CI	28.92, 88.89	39.04, 84.73
	p value	<0.0001	<0.0001
	Value	4 patients (50.0%) with improvement in worst (most) hunger in 24 hours	10 patients (71.4%) with improvement in worst (most) hunger in 24 hours

		RM-493-012	RM-493-015
	90% CI	19.29, 80.71	46.00, 89.60
	p value	0.0004	<0.0001
	Value	5 patients (62.5%) with improvement in average hunger over 24 hours	9 patients (64.3%) with improvement in average hunger over 24 hours
	90% CI	28.92, 88.89	39.04, 84.73
	p value	<0.0001	<0.0001
Statistical test	**Type**	Exact binomial test at a 1-sided 5% significance level, with corresponding 2-sided 90% CIs calculated using the exact Clopper-Pearson method	
Other outcome	**Name**	Secondary endpoint – absolute change in waist circumference from baseline	
	Unit	cm	
Type of analysis	**DUS**	[redacted]	[redacted]
Effect size	**Value**	LS mean [redacted]	LS mean [redacted]
	90% CI	[redacted]	[redacted]
Statistical test	**Type**	Model-based summary statistics from a longitudinal mixed ANOVA with fixed effect for visit, baseline waist circumference and random effect for patient	
	p value	[redacted]	[redacted]
Other outcome	**Name**	Secondary endpoint – comparison of weight change during the double-blind, placebo-controlled withdrawal period	
	Unit	kg	
Type of analysis	**DUS**	[redacted]	[redacted]
Effect size	**Value**	Mean [redacted]	Mean [redacted]
	90% CI	[redacted]	[redacted]
Statistical test	**Type**	Two-sided 90% CI and two-sided p-value from a paired t-test	
	p value	[redacted]	[redacted]

		RM-493-012	RM-493-015
Other outcome	**Name**	Secondary endpoint - reversal of daily hunger reduction during the double-blind, placebo-controlled withdrawal period	
	Unit	Absolute change	
Type of analysis	**DUS**	patients aged ≥12 years, [redacted]	patients aged ≥12 years, [redacted]
Effect size	**Value**	Mean change in morning hunger [redacted]	Mean change in morning hunger [redacted]
	90% CI	[redacted]	[redacted]
	p value	[redacted]	[redacted]
	Value	Mean change in worst (most) hunger in 24 hours [redacted]	Mean change in worst (most) hunger in 24 hours [redacted]
	90% CI	[redacted]	[redacted]
	p value	0.1289	[redacted]
	Value	Mean change in average hunger in 24 hours [redacted]	Mean change in average hunger in 24 hours [redacted]
	90% CI	[redacted]	[redacted]
	p value	[redacted]	[redacted]
Statistical test	**Type**	Two-sided 90% CI and two-sided p-value from a paired t-test	
Other outcome	**Name**	Secondary endpoint – change in body mass and body fat from baseline	
	Unit	g and %	
Type of analysis	**DUS**	[redacted]	[redacted]
Effect size	**Value**	LS mean change in body mass [redacted]	LS mean change in body mass [redacted]
	90% CI	[redacted]	[redacted]
	p value	[redacted]	[redacted]
	Value	LS mean change in body mass [redacted]	LS mean change in body mass [redacted]
	90% CI	[redacted]	[redacted]

		RM-493-012	RM-493-015
	p value	[redacted]	[redacted]
	Value	LS mean change in body fat [redacted]	LS mean change in body fat [redacted]
	90% CI	[redacted]	[redacted]
	p value	[redacted]	[redacted]
	Value	LS mean change in body fat [redacted]	LS mean change in body fat [redacted]
	90% CI	[redacted]	[redacted]
	p value	[redacted]	[redacted]
Statistical test	**Type**	Model-based summary statistics from a longitudinal mixed ANOVA with fixed effect for week, baseline body mass or fat and random effect for patient	
Other outcome	**Name**	Secondary endpoint – change in BMI	
	Unit	%	
Type of analysis	**DUS**	[redacted]	[redacted]
Effect size	**Value**	LS mean [redacted]	LS mean -13.2
	90% CI	[redacted]	[redacted]
Statistical test	**Type**	Model-based summary statistics from a longitudinal mixed ANOVA with fixed effect for week, baseline BMI and random effect for patient	
	p value	[redacted]	[redacted]

9.6.1.3 *Unpublished data for Study RM-493-022*

Study RM-493-022 was a Phase 3 extension study, for patients who completed 1 year of treatment in a prior setmelanotide trial.

POMC/PCSK1 patient change in body weight

Patients with POMC/PCSK1 mutations who continued setmelanotide treatment for an additional approximately 2 years in the extension study demonstrated the ability to maintain the significant and clinically-meaningful weight loss achieved after approximately 1 year of stemelanotide treatment in the index study.

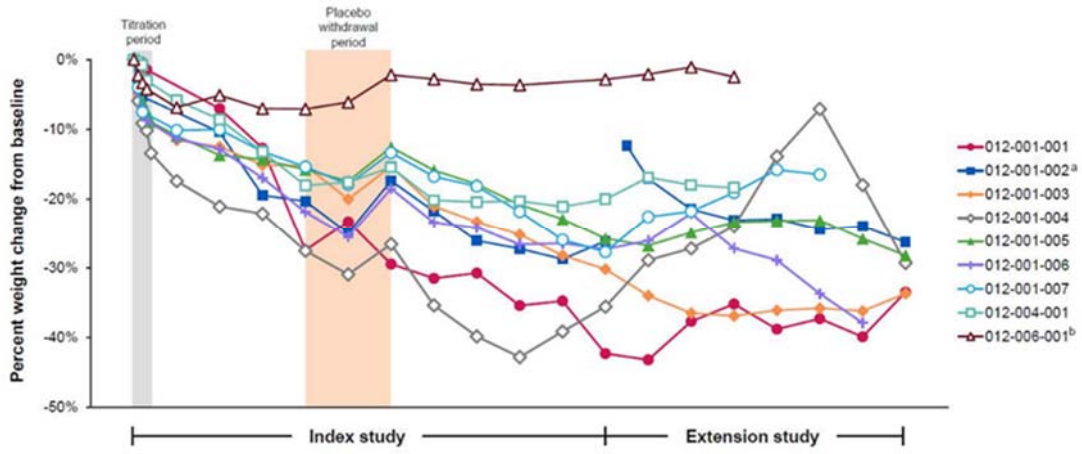
For the 9 patients with POMC/PCSK1 mutations, mean body weight at inclusion in the index study was 114.98 kg and 83.61 kg at inclusion in the extension study, reflecting the significant weight loss achieved during the index study. At the data cut-off date (30 April 2020), the 5 patients who had reached 89 weeks of treatment in the extension study (a total of approximately 141 weeks of treatment) showed weight stabilisation (a mean change of 0.46 kg compared to inclusion in the extension study). Patients had a mean weight of 92.18 kg, a mean weight loss of more than 40 kg from inclusion in the Phase 3 study. The data presented in Table 50 are those available as of the cut-off date in the original report rider (30 April 2020) and are only for patients with POMC/PCSK1 mutations.

Table 50 Mean change in body weight for POMC/PCSK1 patients (Study RM-493-022 Rider data)

	Statistics	Index study POMC/PCSK1 (N=9)	Extension study POMC/PCSK1 (N=9)
Weight at inclusion (kg)	N	9	9
	Average (SD)	114.98 (37.755)	83.61 (22.121)
	95% CI	85.96, 144.00	66.61, 100.61
	Median	114.70	82.70
	Min, Max	55.9, 186.7	54.3, 121.9
Weight at 89 weeks (kg)	N		5
	Average (SD)		92.18 (21.261)
	95% CI		65.78, 118.58
	Median		82.70
	Min, Max		70.5, 124.1
Absolute change from inclusion to 89 weeks (kg)	N	5	5
	Average (SD)	-40.22 (12.619)	-0.46 (13.394)
	95% CI	-55.89, -24.55	-17.09, 16.17
	Median	-35.80	-2.80
	Min, Max	-62.6, -32.5	-19.4, 16.4
Percent change from inclusion to 89 weeks (%)	N	5	5
	Average (SD)	-30.20 (3.285)	0.14 (12.387)
	95% CI	-34.28, -26.12	-15.24, 15.52
	Median	-29.30	-3.30
	Min, Max	-33.7, -26.3	-15.9, 15.2

Figure 17 shows the evolution of the body weight of the 9 POMC/PCSK1 patients from the inclusion of the patients in the index study to the cut-off date of the amendment (30 April 2020).

Figure 17 Mean change in body weight for POMC/PCSK1 patients (Study RM-493-022 Rider data)



LEPR patient change in body weight

Three patients with LEPR deficiency from study RM-493-015 (Patients 015-003-001, 015-003-002 and 015-003-003) had an abnormally high setmelanotide concentration that was inconsistent with the weight change observed in these 3 patients during the 52-week Phase 3 study. The sponsor hypothesised that these 3 patients had incorrectly administered study drug and not followed the prescribed regimen. They did not achieve the primary objective of the index study (10% weight loss after approximately 52 weeks of treatment). In addition, these 3 patients required an interruption of setmelanotide treatment after completion of the Phase 3 study and before inclusion into the extension study. These patients gained significant weight during this period (approximately 4.5 months) without setmelanotide treatment. In addition, the investigator re-initiated treatment for these 3 LEPR patients at lower doses (lower than the established therapeutic dose) and at 25 weeks, each of these patients was receiving lower doses than at the end of the index study (data on file, Rhythm Pharmaceuticals).

The mean body weight for the 6 LEPR patients on inclusion in the index study was 125.43kg and at the last index study measurement was 110.23kg; the mean body weight of the 6 LEPR patients at inclusion into the extension study was 121.87kg. At Week 25 of the extension study, the mean body weight of the 6 LEPR patients was 120.28 kg, a mean change of -1.58 kg from inclusion into the extension study and -5.15 kg from inclusion into the index study. The mean percent change in body weight for each individual was -1.77% from inclusion in the extension study and -4.13% from inclusion in the index study.

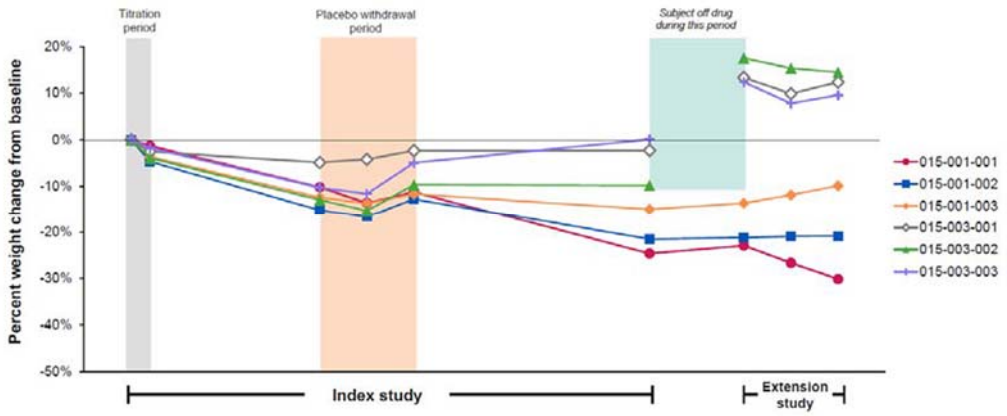
Two of the 3 LEPR patients without treatment interruption continued losing weight during the extension study; the weight of the third stabilised (an increase of about 4%) during the extension study. Change in body weight at inclusion and at the last visit of LEPR patients are presented in Table 51.

Table 51 Mean change in body weight for LEPR patients (Study RM-493-022 Rider data)

	Statistics	Index study (N=6)	Extension study (N=6)
Weight at inclusion (kg)	N	6	6
	Average (SD)	125.43 (30.695)	121.87 (35.968)
	95% CI	93.22, 157.65	84.12, 159.61
	Median	118.00	118.05
	Min, Max	89.4, 170.4	81.4, 173.8
Weight at 89 weeks (kg)	N		6
	Average (SD)		120.28 (38.052)
	95% CI		80.35, 160.22
	Median		115.00
	Min, Max		81.8, 172.3
Absolute change from inclusion to 25 weeks (kg)	N	6	6
	Average (SD)	-5.15 (22.904)	-1.58 (4.964)
	95% CI	-29.19, 18.89	-6.79, 3.63
	Median	-4.20	-2.00
	Min, Max	-36.4, 18.9	-8.7, 6.4
Percent change from inclusion to 25 weeks (%)	N	6	6
	Average (SD)	-4.13 (18.938)	-1.77 (4.552)
	95% CI	-24.01, 15.74	-6.54, 3.01
	Median	-0.20	-1.70
	Min, Max	-30.2, 14.4	-9.4, 4.4

Figure 18 shows the evolution of the body weight of the 6 LEPR patients from the inclusion of the patients in the index study to the cut-off date (30 April 2020).

Figure 18 Mean change in body weight for LEPR patients (Study RM-493-022 Rider data)



POMC/PCSK1 patient change in hunger score

At the time of data freeze (30 April 2020), 7 of the 9 POMC/PCSK1 patients were aged ≥12 years: the mean hunger score for these 7 POMC/PCSK1 patients was 8.0 at inclusion in the index study and 6.4 at inclusion in the extension study. During the extension study, mean hunger score remained constant for these 7 patients: at 37 weeks mean hunger score was 6.3 and for the 5 patients who completed treatment to 89 weeks the hunger score was 7.0. The results presented in Table 52 are based on the database freeze for the initial report (09 May 2019).

Table 52 Mean change in hunger score for POMC/PCSK1 patients (Study RM-493-022 baseline data)

	Statistics	Index study POMC/PCSK1 (N=7)	Extension study POMC/PCSK1 (N=7)
Hunger score at inclusion	N	7	7
	Average (SD)	8.00 (0.816)	6.43 (2.637)
	95% CI	7.24, 8.76	3.99, 8.87
	Median	8.00	7.00
	Min, Max	7.0, 9.0	2.0, 10.0
Hunger score at 37 weeks	N		5
	Average (SD)		6.80 (1.789)
	95% CI		4.58, 9.02
	Median		8.00
	Min, Max		4.0, 8.0
Absolute change from inclusion to 37 weeks	N	5	5
	Average (SD)	-1.00 (2.550)	-0.20 (3.421)
	95% CI	-4.17, 2.17	-4.45, 4.05
	Median	0.00	1.00
	Min, Max	-5.0, 1.0	-6.0, 3.0
Percent change from inclusion to 37 weeks (%)	N	5	5
	Average (SD)	-10.397 (29.9128)	6.857 (43. 4999))
	95% CI	-47.539, 26.745	-47.155, 60.869
	Median	0.000	14.286
	Min, Max	-55.56, 14.29	-60.00, 60.00

LEPR patients change in hunger score

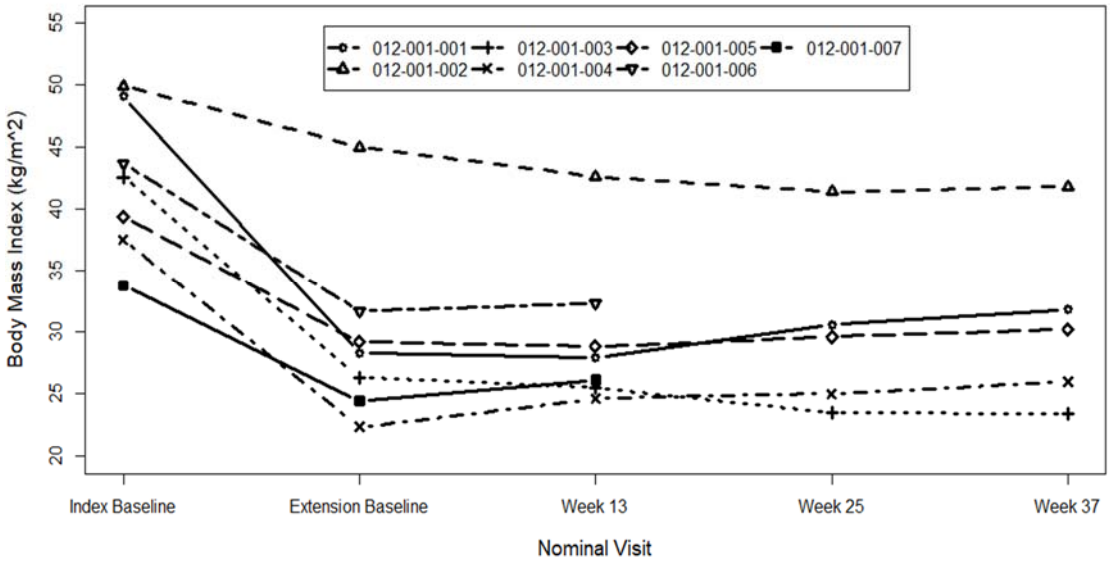
At the date of the rider data freeze (30 April 2020), for the 6 LEPR patients the mean hunger score was 7.1 on inclusion into the index study and 5.7 on inclusion into the extension study. During the extension study mean hunger score remained constant for the 6 LEPR patients (5.7 at 25 weeks). These

results are observed as of the database freeze (cut-off) of the original report rider (30 April 2020).

POMC/PCSK1 patient change in BMI

After approximately 9 months of additional treatment with setmelanotide in the extension study, patients with POMC/PCSK1 mutations maintained the decrease in body mass index achieved after approximately 1 year of treatment with setmelanotide in the index study. The results presented in Figure 19 are from the cut-off date for the initial report (09 May 2019).

Figure 19 Change in body mass index in POMC/PCSK1 patients (Study RM 493-022 baseline data)



POMC/PCSK1 patient change in waist size

After approximately [redacted] months of additional treatment with setmelanotide in the extension study, patients with POMC/PCSK1 mutations [redacted] in waist circumference and [redacted] in waist circumference achieved after approximately 1 year of treatment with setmelanotide in the index study. Results presented (**Error! Not a valid bookmark self-reference.**) are as of the cut-off date for the initial report (09 May 2019).

Table 53 Change in waist circumference for POMC/PCSK1 patients (Study RM 493-022 baseline data)

	Statistics	Index study (N=[redacted])	Extension study (N=[redacted])
Waist circumference at inclusion	N	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Waist circumference at 37 weeks (cm)	N	[redacted]	
	Average (SD)	[redacted]	
	95% CI	[redacted]	
	Median	[redacted]	
	Min, Max	[redacted]	
Absolute change from inclusion to 37 weeks (cm)	N	[redacted]	[redacted]
	Average (SD)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Percent change from inclusion to 37 weeks (%)	N	[redacted]	
	Average (SD)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Figure 20 shows change in waist circumference for the 7 POMC/PCSK1 patients from inclusion in the index study to the date of the database freeze (cut-off) for the initial data (09 May 2019).

Figure 20 Change in waist circumference for POMC/PCSK1 patients (Study RM 493-022 baseline data)

9.6.2 Inclusion of efficacy outcomes from analyses other than intention-to-treat

According to FDA guidance, the FAS is as close as possible to the ITT population for studies conducted in patients with rare diseases (https://rarediseases.info.nih.gov/files/vali.pdf).

The secondary endpoints percent change from baseline in body weight at the end of approximately 1 year of treatment and mean percent change from baseline in weekly average hunger were evaluated using the DUS, defined as patients who received study drug, demonstrated loss of ≥5 kg or ≥5% (if baseline weight was <100 kg) in body weight over the 12-week open-label treatment period, and proceeded into the double-blind, placebo-controlled withdrawal period. This was deemed appropriate as it is representative of how setmelanotide will be used in clinical practice, where patients who fail to achieve the required 5 kg or 5% weight loss at the end of the 12-week titration period will cease treatment.

9.7 Adverse events

9.7.1 Identification of studies assessing adverse events

9.7.1.1 *Published studies*

The search findings described in Section 9.2.1 were also assessed to consider adverse events (AEs) associated with setmelanotide treatment.

9.7.1.2 *Unpublished studies*

The safety and tolerability of setmelanotide treatment was reported as a primary endpoint for Study RM-493-022 and as a secondary endpoint for Studies RM-493-012, RM-493-015 and RM-493-011; safety data were summarised using descriptive statistics for all trials. Adverse events of special interest in setmelanotide trials were either events that commonly occur during setmelanotide treatment (darkening of skin, sexual events, nausea, vomiting and injection site reactions), potential mechanistic-related events such as hypertension, or events associated with the disease indication such as depression and suicidal ideation.

9.7.2 Important adverse events

9.7.2.1 *Published studies*

Setmelanotide was well tolerated. The Phase 3 studies reported similar rates of serious adverse events (SAEs, Table 54), with none being considered treatment-related. No SAEs were reported in the Phase 2 study. Frequently reported adverse events (AEs) included injection-site reactions, changes to skin pigmentation and nausea. In the Phase 3 trials, skin pigmentation was more common in the POMC than the LEPR population. Across all studies, only 1 patient discontinued study medication due to a treatment-related AE.

Table 54 Summary of safety results from published studies

	Number of patients			
	Clément 2020 (RM-493-012) (N=10) (55)	**Clément 2020 (RM-493-015) (N=11) (55)**	**Kühnen 2016 (RM-493-011) (N=2)(54)**	**Clément 2018 (RM-493-011) (N=3) (27)**
Serious AEs	4	3	0	0
Serious treatment-related AEs	0	0	-	-
Treatment-related AEs	10	11	-	-
Injection site reaction	10	11	-	-
Skin and subcutaneous disorders related to hyperpigmentation	10	5	-	-
Skin hyperpigmentation	10	4	-	-
Pigmentation disorder	0	4	-	-
Skin discolouration	0	2	-	-
Nausea	5	4	1	1
Vomiting	3	0	-	-
Dry mouth	-	-	2	3
Headache	-	-	1	3
Diarrhoea	-	-	1	-
Upper airway infection	-	-	1	-
Bone and muscular pain	-	-	1	2
Pain at injection site	-	-	1	2
Sadness/emptiness	-	-	2	-
Hyperventilation	-	-	1	-
Shivering	-	-	1	-
Reduced appetite	-	-	2	3
Increased skin pigmentation	-	-	2	-
Induration at injection site	-	-	1	2
Tiredness	-	-	1	-
Skin folliculitis	-	-	-	1
Increased tanning of skin/nevi	-	-	-	3
Abdominal pain	-	-	-	1

9.7.2.2 *Unpublished study RM-493-012*

Safety data are based on an addendum to the clinical study report dated 22 May 2020 (data cut-off 30 April 2020).

[redacted] patients ([redacted]%) treated with setmelanotide in Study RM-493-012 were reported with at least 1 treatment-emergent adverse event (TEAE) and at least 1 TEAE that was considered related to the study drug (**Error! Not a valid bookmark self-reference.**); [redacted] patients ([redacted]%) were reported with an SAE during the study, [redacted] of which were considered related to study drug. There were no TEAEs leading to study drug withdrawal and no deaths during this study.

Table 55 Overview of treatment-emergent adverse events in Study RM 493-012 (SAS)

Event	Number (%) of patients (N = [redacted])
TEAE	[redacted]
Serious TEAE	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to death	[redacted]

The TEAEs reported in Study RM-493-012 were generally mild and commonly related to ongoing skin hyperpigmentation or injection site reactions (Table 56).

Table 56 Frequent (≥20% of patients) adverse events reported in patients treated with setmelanotide in Study RM 493-012 (SAS

Preferred term	Number (%) of patients (N = [redacted])
Skin hyperpigmentation	[redacted]
Injection site erythema	[redacted]
Injection site oedema	[redacted]
Injection site pruritus	[redacted]
Nausea	[redacted]
Vomiting	[redacted]
Headache	[redacted]
Upper respiratory tract infection	[redacted]
Melanocytic naevus	[redacted]
Fatigue	[redacted]
Back pain	[redacted]
Diarrhoea	[redacted]
Abdominal pain	[redacted]
Dry mouth	[redacted]
Injection site pain	[redacted]
Dry skin	[redacted]
Chills	[redacted]
Alopecia	[redacted]
Asthenia	[redacted]
Vertigo	[redacted]

Events of special interest were commonly injection-site reactions, nausea, vomiting and skin hyperpigmentation. [redacted] patients ([redacted]%) experienced skin hyperpigmentation, [redacted] patients ([redacted]%) were reported with injection site reaction events, [redacted] patients ([redacted]%) each with nausea or vomiting, [redacted] patients ([redacted]%) with suicidal ideation, and * patients each ([redacted]%) with depression or sexual events.

9.7.2.3 *Unpublished study RM-493-015*

[redacted] patients ([redacted]%) treated with setmelanotide in Study RM-493-015 were reported with at least 1 TEAE (**Error! Not a valid bookmark self-reference.**); [redacted] patients ([redacted]%) were reported with an SAE during the study, none of which were considered related to study drug. [redacted] was reported with a TEAE leading to study drug withdrawal and a one with a TEAE leading to death; [redacted] was considered related to setmelanotide treatment, the death was also not considered related.

Table 57 Overview of treatment-emergent adverse events in Study RM 493-015 (SAS)

Event	Number (%) of patients (N = [redacted])
TEAE	[redacted]
Serious TEAE	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to death	[redacted]

The TEAEs reported in Study RM-493-015 were commonly related to skin hyperpigmentation, injection site reactions and nausea (Table 58).

Table 58 Frequent (≥20% of patients) adverse events reported in patients treated with setmelanotide in Study RM 493-015 (SAS)

Preferred term	Number (%) of patients (N = [redacted])
Injection site erythema	[redacted]
Skin hyperpigmentation	[redacted]
Injection site pruritus	[redacted]
Nausea	[redacted]
Injection site induration	[redacted]
Injection site pain	[redacted]
Diarrhoea	[redacted]
Injection site oedema	[redacted]
Injection site bruising	[redacted]
Headache	[redacted]
Asthenia	[redacted]
Abdominal pain upper	[redacted]
Nasopharyngitis	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
Insomnia	[redacted]
Dizziness	[redacted]
Spontaneous penile erection	[redacted]
Influenza-like illness	[redacted]
Injection site hypersensitivity	[redacted]
Muscle spasm	[redacted]
Anxiety	[redacted]
Anaemia	[redacted]

Events of special interest reported were commonly injection-site reactions, nausea, and skin hyperpigmentation. [redacted] patients ([redacted]%) were reported with an injection site reaction event, [redacted] patients ([redacted]%) with disorder, [redacted]

patients ([redacted]%) were reported with nausea, [redacted] patients ([redacted]%) each with depression and sexual events, [redacted] patients ([redacted]%) with vomiting, and [redacted] with suicidal ideation.

9.7.2.4 *Unpublished study RM-493-011*

[redacted] patients ([redacted]%) treated with setmelanotide in Study RM-493-011 were reported with at least 1 TEAE and at least 1 TEAE that was considered related to the study drug (**Error! Not a valid bookmark self-reference.**); [redacted] patients ([redacted]%) were reported with an SAE, neither of which was considered related to study drug. There were no TEAEs leading to study drug withdrawal and no deaths.

Table 59 Overview of treatment-emergent adverse events in Study RM 493-011 (SAS)

Event	Number (%) of patients (N = [redacted])
TEAE	[redacted]
Serious TEAE	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to death	[redacted]

The TEAEs reported in this study were most commonly dry mouth, skin hyperpigmentation, headache or injection site reactions (Table 60).

Table 60 Frequent (≥20% of patients) adverse events reported in patients treated with setmelanotide in Study RM 493-011 (SAS)

Preferred term	Number (%) of patients (N = [redacted])
Dry mouth	[redacted]
Skin hyperpigmentation	[redacted]
Headache	[redacted]
Injection site erythema	[redacted]
Injection site pain	[redacted]
Nausea	[redacted]
Upper respiratory tract infection	[redacted]
Fatigue	[redacted]
Abdominal pain	[redacted]
Pain in extremity	[redacted]
Depressed mood	[redacted]

The events of special interest reported were injection-site reactions ([redacted] patients, [redacted]%), nausea ([redacted] patients, [redacted]%) and skin hyperpigmentation ([redacted] patients, [redacted]%).

9.7.2.5 *Unpublished study RM-493-022*

[redacted] patients ([redacted]%) treated with setmelanotide in Study RM-493-022 were reported with at least 1 TEAE (Table 61); [redacted] each was reported with an SAE or TEAE leading to study drug withdrawal and there were no deaths.

Table 61 Overview of treatment-emergent adverse events in Study RM-493-022

Event	Number (%) of patients (N = [redacted])
TEAE	[redacted]
Serious TEAE	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to death	[redacted]

Common TEAEs reported in this study were upper respiratory tract infection, headache, nasopharyngitis and fatigue (Table 62).

Table 62 Frequent (≥20% of patients) adverse events reported in patients treated with setmelanotide in Study RM 493-022 (Safety Analysis Set)

Preferred term	Number (%) of patients (N = [redacted])
Upper respiratory tract infection	[redacted]
Headache	[redacted]
Nasopharyngitis	[redacted]
Fatigue	[redacted]
Injection site erythema	[redacted]
Alopecia	[redacted]
Vertigo	[redacted]

9.7.3 Overview of the safety of the technology

The setmelanotide safety database for patients with POMC/PCSK1- or LEPR-deficiency obesity comprises the 37 patients treated in Phase 2 and 3 studies; of these, 6 paediatric patients (aged <12 years) were included in pivotal studies. Some of these patients continued treatment in the long-term extension study and a few have had ongoing setmelanotide treatment for

almost 2 years. The limited size of the safety population reflects the orphan nature of the treatment indication. However, additional supportive safety data are available for setmelanotide in other obesity populations, comprising a total of 377 exposed patients.

Treatment with setmelanotide was well tolerated in POMC/PCSK1- or LEPR-deficiency patients with severe obesity. The most common adverse events seen during setmelanotide treatment in Phase 2/3 trials were skin hyperpigmentation, injection site erythema, nausea, headache, injection site pruritus, injection site oedema, and injection site pain. Other events occurring in >20% of patients were diarrhoea, fatigue, injection site induration, vomiting, back pain, dry mouth, and upper respiratory tract infection. Injection-site reactions, nausea and dry mouth were considered related to setmelanotide treatment. Specific analysis of sexual events identified that some male patients had spontaneous, transient penile erection during setmelanotide dosing.

The safety profile in the long-term extension study was consistent with that seen in the Phase 2/3 studies, with the most common events being upper respiratory tract infection, headache, nasopharyngitis and fatigue. The frequency of injection site reactions was lower in the extension study. Injection-site reactions and alopecia were commonly considered related to setmelanotide treatment. Skin hyperpigmentation was present for many patients when they entered Study RM-943-022 but did not worsen during prolonged setmelanotide exposure.

Specific analyses did not identify any increase in heart rate or blood pressure or worsening of depression or suicidal ideation in patients with POMC/PCSK1- or LEPR-deficiency obesity treated in Phase 2/3 studies.

Individuals with POMC and LEPR-deficiency obesity show extensive evidence of the effects of severe obesity on their health. Frequent comorbidities include lipid abnormalities; sleep apnoea; leg, hip, and knee fracture/malformation/ arthritis; and delayed growth and pubertal development. Adrenal insufficiency, severe hormonal abnormalities, and infection risk can add to the seriousness

and potentially life-threatening nature of POMC- and LEPR-deficiency obesity. Any assessment of the safety of setmelanotide needs to take into account the increased risk associated with comorbidities and associated medications.

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis.

Evidence synthesis was not feasible given that no trials were identified that provided estimates of treatment effect on the outcomes of interest for the comparator standard of care.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review.

Systematic literature review identified no evidence on the effectiveness and safety of standard of care treatment for patients with LEPR/PPL related obesity; all three studies identified by the SLR were single arm setmelanotide trials. Hence, no direct evidence on relative treatment effects was available and due to a lack of evidence on treatment effects for relevant comparators it was not possible to conduct any indirect assessment of relative treatment effects.

Patients treated with setmelanotide in the Phase 3 trials experienced significant weight loss over the treatment period. The mean change in body weight from baseline to week 52 was 25.6% in the POMC trial ($p<0.0001$) and 12.5% in the LEPR trial ($p<0.0001$)(55). BMI also improved significantly in both populations decreasing by 27.8% in the POMC trial and 13.1% in the LEPR trial, at 52 weeks compared to baseline ($p<0.0001$). Patients in both populations also showed decreased waist circumference at final follow-up (-14.9% [$p<0.0001$] and -7.2% [$p=0.0002$], respectively)(55).

Similar efficacy results were observed in the Phase 2 case series. Two patients with POMC defects lost 13.4% and 16.6% of their initial body weight at 12- and 13-week follow-up, respectively. [redacted] continued to lose weight over the extended follow-up period, achieving weight loss of [redacted]% of their initial body weight at 42-week follow-up. BMI was reduced by [redacted]% and [redacted]% in the [redacted] patients at [redacted] follow-up, respectively(54). In the LEPR case series, follow-up intervals varied. Subjects lost between [redacted]% and [redacted]%

of their baseline body weight over the treatment period, ranging from [redacted] weeks, respectively(27).

The Phase 3 studies showed that blood pressure remained stable throughout the 52-week setmelanotide treatment course in both POMC and LEPR populations. Lipid profiles showed a significant reduction in circulating triglycerides, compared with baseline, in the POMC trial (−36.6%) but not the LEPR trial (−7.0%). Both trial populations experienced a reduction in LDL cholesterol, although results were only significant in the LEPR population (POMC: -7.6 and LEPR -10.0%). Both trials reported a reduction in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at final follow-up although neither trial reported observed changes in AST/ALT ratios (55). In the Phase 2 case series, both patients with POMC genetic defects had a reduction in LDL cholesterol compared to baseline, one patient with longer-term follow-up also showed a reduction in circulating triglycerides (54). All three patients with LEPR defects, showed reduced triglycerides at final follow-up, whereas only one patient had a reduction in LDL cholesterol(27).

Setmelanotide was well tolerated by the treated subjects. The Phase 3 trials reported similar rates of serious AEs, however none of the serious AEs were treatment-related(55). No serious AEs were reported in the Phase 2 study. Frequently reported AEs included injection site reactions, changes to skin pigmentation and nausea (27, 54, 55). In the two larger trials, skin pigmentation was more common in the POMC population than in the LEPR trial. Across all studies, only one patient discontinued treatment due to a treatment-related AE(55).

The three setmelanotide studies were overall considered to be high quality. Although, there were some concerns about the potential impact of confounding factors on treatment outcomes, as none of the studies identified potential effect modifiers and none adjusted for confounding factors in the analyses.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events

from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The clinical development program for IMCIVREE® (setmelanotide) was based primarily on:

- Two Phase 3 studies (RM-493-012 and RM-493-015) were non-randomised, open-label, multicenter studies designed to evaluate the effects of setmelanotide on body weight change after 1 year of treatment in patients with obesity associated with rare biallelic POMC, PCSK1 (RM-493-012) or LEPR (RM-493-015) deficiency or mutation-related loss of function.
- A long-term extension study (RM-493-022), up to 2 years, in patients who completed a previous study with a setmelanotide treatment phase in the management of MC4R pathway-related genetic obesity disorders.

The studies included two cohorts of patients: a pivotal cohort and a supplemental cohort, the latter of which was formed after the pivotal cohort. The primary efficacy analysis was based on patients in the pivotal cohort.

Most patients included in these studies were of European origin:

- In Study RM-493-012: 13 of 15 patients (86.7%) in the combined cohorts were from French (1 patient in the pivotal cohort and 1 in the supplemental cohort; 15.4% of European patients), German (7 patients in the pivotal cohort), Spanish (2 patients in the supplemental cohort), and Belgian (2 patients in the supplemental cohort) centres.
- In Study RM-493-015: 14 of 15 patients (93.3%) in the combined cohorts were from centres in France (4 patients in the pivotal cohort and 2 in the supplemental cohort; 42.9% of European patients), Germany (3 patients in the pivotal cohort and 1 in the supplemental cohort), the Netherlands (3 patients in the pivotal cohort), and the United Kingdom (1 patient in the pivotal cohort).

At study entry, the mean weight of patients in the pivotal cohort with POMC/PCSK1 deficiency was 118.7 kg (mean age 18.4 years) and for patients with LEPR deficiency 133.3 kg (mean age 23.7 years).

The primary endpoint was the proportion of patients in the FAS who showed at least a 10% reduction in weight at approximately 1 year of treatment from baseline. This criterion was ambitious: generally, a threshold between 5% and 10% is used in studies, according to FDA and EMA recommendations. In the absence of treatment, these patients continue to gain weight throughout their lives, with an average weight gain of 7 to 8 kg/year (mainly analysed on the basis of historical data of patients included in these studies).

IMCIVREE® (setmelanotide) demonstrated efficacy and safety in both of these studies, with the key primary and secondary endpoints significantly met:

- Regarding the primary endpoint:
  - In total, 85.7% (12 of 14; 90% CI 61.46, 97.40) of POMC/PCSK1 patients and 53.3% (8 of 15; 90% CI 30.00, 75.63) of LEPR patients in the combined cohorts showed at least a 10% weight loss from inclusion to 52 weeks ($p<0.0001$) The results observed in the pivotal cohort were consistent with those of the combined cohorts: 80% (90% CI 49.31, 96.32) of POMC/PCSK1 patients (8 of 10) and 45.5% (90% CI 19.96, 72.88) of LEPR patients (5 of 11) showed at least 10% weight loss from inclusion to 1 year ($p<0.0001$ in both studies).
  - In the POMC/PCSK1 study, 7 of 10 patients in the pivotal cohort experienced weight loss of ≥25%.
  - Based on a response rate to the primary end point of 63% for the combined LEPR and POMC/PCSK1 populations, the NNT is 1.6 assuming a split between the LEPR and POMC/PCSK1 of 2:1, respectively. This is likely to be a conservative estimate since the primary endpoint response rate measures weight loss compared to baseline, which in children and adolescents who are still growing and would thus be expected to gain weight between baseline and 52 weeks (even if non-obese), is not an appropriate measure of clinical

effectiveness. A weight loss of e.g. 6% in these patients while gaining significant height, and thus a significant reduction in BMI-Z, and with decrease in hunger score would be considered a clinical success despite not meeting the trial primary endpoint. The NNH is not quantifiable given there were no treatment related severe adverse events reported.

- Regarding the key secondary endpoints:
  - A significant reduction in mean body weight of -25.83% from baseline to 52 weeks ($p<0.0001$) was seen for the 13 POMC/PCSK1 patients and of -12.34% ($p<0.0001$) was seen for the 10 LEPR patients in the combined DUS cohorts. The results observed in the pivotal cohort were consistent with those for the combined cohorts: a mean weight reduction of 25.56% in the 9 POMC/PCSK1 patients (83.1 kg vs. 114.97 kg) and 12.47% (115.0 kg vs. 131.7 kg) in the 7 LEPR patients after approximately 52 weeks of setmelanotide treatment, with both being statistically significant compared with baseline ($p<0.0001$).
  - A mean decrease in highest hunger score of 42.7% ($p<0.0001$) for the 10 LEPR patients in the combined cohorts and 27.1% for the 7 POMC/PCSK1 patients (5.8 vs 8.1 $p=0.0005$) aged ≥12 years was seen for the pivotal cohort DUS. The results observed in the pivotal cohort were consistent with those of the combined cohorts, with a mean decrease in highest hunger score of 43.7% in the 7 LEPR patients (4.1 vs. 7.0 $p<0.0001$), from inclusion to approximately 52 weeks of setmelanotide treatment.
  - An improvement of ≥25% in highest hunger score for 10 of 14 LEPR patients (71.4%; CI 90% 46.00, 89.60; $p<0.0001$) in the combined cohorts and in 4 of 8 POMC/PCSK1 patients (50%; $p=0.0004$) aged ≥12 years was seen in the pivotal cohort FAS. Results for the pivotal cohort were consistent with those in the combined cohorts with ≥25% improvement in highest hunger score in 8 of 11 LEPR patients (72.7%; $p<0.0001$) from baseline to approximately 52 weeks of treatment.
- Regarding change in BMI:

- A mean decrease of [redacted]% in mean BMI for POMC/PCSK1 patients meant that overall they transitioned from severe obesity (mean BMI at inclusion of 39.0 kg/m^2) to overweight (mean BMI of 27.8 kg/m^2) after 1 year of treatment [redacted]
- A mean decrease of [redacted]% in mean BMI for LEPR patients meant that overall, they transitioned from massive obesity (mean BMI at inclusion of 47.5 kg/m^2) to severe obesity (mean BMI of 38.8 kg/m^2) after 1 year of treatment [redacted].

- Improvements were also observed for all other secondary, tertiary and exploratory endpoints using the DUS:
  - A mean change in mean waist circumference of -14.90% (18.39 cm, p<0.0001) was seen in the 9 POMC/PCSK1 patients and of -7.24% (9.10 cm, p=0.0001) for the 7 LEPR patients, from inclusion to approximately 52 weeks of setmelanotide treatment

- A withdrawal effect was seen for setmelanotide treatment, with a mean weight loss of 3.0 kg during the 4 weeks of treatment with setmelanotide vs. an increase of 5.5 kg during the 4 weeks of placebo administration; the significant difference between the two periods equated to 8.5 kg (p=0.0029) for 8 of the 9 POMC/PCSK1 patients. Similarly, for LEPR patients, there was a mean weight loss of 2.1 kg during the 4 weeks of setmelanotide treatment vs. an increase of 5.0 kg during the 4 weeks of placebo administration; the significant difference between the two periods equated to 7.0 kg (p=0.0014) for 7 of the 9 patients
- Overall, 75.6% of body weight loss observed in POMC/PCSK1 patients was from body fat, considering an average loss of 20.3 kg of body fat for an average body mass loss of 26.9 kg; body mass reduced by 23.90% while body fat reduced by 38.64%. It should be noted that there was no loss of bone density and minimal loss of non-bone lean body mass. Similarly, in LEPR 67.3% of body weight loss was from body fat, considering an average loss of 8.7 kg of body fat for an average body mass loss of 12.9 kg; body mass reduced by 11.05% while body fat reduced by 15.03%.

[redacted]POMC/PCSK1 patients had a reduction in BMI and, with the exception of patients [redacted], also had a reduction of at least [redacted] BMI severity stage after 52 weeks of setmelanotide treatment; [redacted]% of patients [redacted] had a reduction of at least 2 BMI severity stages and [redacted] had a reduction of at least 3 BMI severity stages. [redacted] progressed through [redacted] BMI severity stages.

It is worth noting that [redacted]% [redacted] of patients achieved a [redacted] after 52 weeks of treatment; all apart from [redacted] patients [redacted] had BMI equivalent to or lower than [redacted] obesity after setmelanotide treatment.

[redacted] LEPR patients had a reduction in BMI, with [redacted] having a reduction of at least one BMI severity stage after 52 weeks of setmelanotide treatment and [redacted] a reduction of at least BMI severity 2 stages.

An improvement in quality of life was seen for patients in the pivotal cohorts treated with setmelanotide:

- A mean [redacted]% increase in total IWQOL-Lite score [redacted] was seen for the [redacted] POMC/PCSK1 patients aged ≥18 years and a mean [redacted]% increase in score for the 4 LEPR patients aged ≥18 years [redacted]. The respective differences of [redacted] than the suggested MCID (64, 65), emphasising the clinical relevance of the treatment effect
- A significant mean improvement of [redacted]% in total PedsQL score [redacted] as assessed by children and [redacted]% in score [redacted] as assessed by parents for [redacted] POMC/PCSK1 patients aged 8 and 12 years
- A significant mean improvement of [redacted]% in total PedsQL score [redacted] as assessed by children and [redacted]% in score [redacted] as assessed by parents for [redacted] POMC/PCSK1 patients aged 13 to 18 years

As of the date of the database freeze (cut-off) for data for supplemental patients (30 April 2020), quality-of-life data for LEPR patients were not available for the paediatric population.

The long-term extension study showed [redacted] of setmelanotide on weight loss and hunger score reduction up to [redacted] for POMC/PCSK1 patients and up to [redacted] for LEPR patients (at the rider data cut-off date of 30 April 2020).

Overall, treatment with setmelanotide was well tolerated and treatment-emergent AEs reported in these studies were generally mild in intensity. All patients experienced at least 1 AE, the most common being skin hyperpigmentation or transient injection site reactions.

[redacted] POMC/PCSK1 patients reported [redacted] SAEs during the study, [redacted] of which were related to setmelanotide. Serious adverse events were each reported for [redacted] patients [redacted] and comprised depression, major depression, panic attack, acute adrenal insufficiency, pneumonia, hypoglycaemia and pleurisy.

[redacted] LEPR patients reported [redacted] SAEs during the study, [redacted] of which were related to setmelanotide. Serious adverse events were each reported for [redacted] patients [redacted] and comprised cholecystitis, suicidal ideation, and reversible gastric band.

In addition, a motor vehicle accident led to the death of one LEPR patient but was not considered related to study treatment.

In addition, a motor vehicle accident led to the death of one LEPR patient but was not considered related to study treatment.

With the exception of one LEPR patient in the pivotal cohort, who was withdrawn from the study due to Grade 1 eosinophilia, considered by the investigator to be probably related to the treatment, and the patient who died due to motor vehicle accident, there were no reports of treatment discontinuation due to AEs.

No cardiovascular signals were identified in this study, in particular no hypertension or increased heart rate were seen. Given the health status of this severely obese population, ongoing monitoring for depression and

suicidal ideation demonstrated that setmelanotide treatment did not cause or worsen these conditions. In addition, patients reporting such events during the study had a history of depression or mood disorder.

There were no new signals were identified regarding the tolerability of setmelanotide in the long-term study.

IMCIVREE® (setmelanotide) has a favourable efficacy/adverse event ratio and therefore addresses an important unmet medical need for patients with obesity related to a genetic deficiency in POMC, PCSK1 or LEPR; setmelanotide helped meet the disease-management objectives for these patients, such as:

- the impact of binge eating on quality of life
- reduction of weight, BMI and body fat
- reducing comorbidities by reducing the duration of obesity.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

POMC/LEPR-deficiency obesity are rare diseases and enrolment of large numbers of participants into setmelanotide clinical trials was not feasible. A typical randomised, placebo-controlled clinical trial could therefore not be conducted and the small studies that were had limited statistical power. To facilitate the generation of some placebo-controlled data each patient underwent a placebo-controlled withdrawal interval during pivotal trials, with the effect of 4-week withdrawal of setmelanotide dosing assessed for key efficacy parameters (change in body weight and hunger score).

There are no validated instruments for assessing hyperphagia in patients with rare genetic diseases of obesity, and so a Likert-type (0-10) scale was used as part of the daily hunger questionnaire for adults.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope.

The evidence base reflects the scope of the appraisal in that it provides data on the key outcomes of interest in the patient population of interest. The trials were single arm studies and so do not provide comparative data.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice

No factors have been identified that would affect the external validity of study results. Patients in the studies were identified through genetic testing, as per setmelanotide's licence and as would be the case in clinical practice. Study visits occurred every 6 weeks, which may be slightly more frequently than would occur in routine clinical practice, however, patients would be monitored closely on initiation of treatment (at least every 12 weeks).

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

In line with the licenced indication, all patients who are initiated on setmelanotide will require confirmation of POMC/PCSK1 or LEPR deficiency through genetic testing. In practice, patients will be identified for genetic testing by the presence of extreme early onset obesity (before 5 years of age) and that have clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and /or a family history of extreme obesity (67).

10 Measurement and valuation of health effects

10.1 Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

Given the rare nature of the disease under study, published data concerning its implications on HRQL are not available. Key opinion leader opinion is that the main contributors to reduced HRQL are hyperphagia and obesity, including the comorbidities associated with obesity such as sleep apnoea, joint/movement problems and diabetes.

The literature can inform on the implications of obesity on quality of life in the general population. Reports have shown that: individuals with obesity have significantly lower HRQL than those in the normal weight range even for those without chronic conditions known to be associated with obesity (68); the reduction in HRQL seen in those considered severely obese is considered clinically meaningful. An extreme increase in adiposity impacts on quality of life (69), specifically in areas of: physical function, self-esteem, public distress and work when assessed using IWQOL-Lite; and mobility, self-care, and

performing usual activities using EQ5D-3L subscales. Various studies have indicated that obesity and anxiety/depressive disorder often co-occur and are bidirectionally inter-related (70); in such individuals the combined effects of obesity and depressive/anxiety disorders on physical and mental quality of life are thought to be greater than the sum of their separate effects.

It should be stressed that genetic obesity is not directly comparable to general obesity in terms of QoL. The impact of the duration of obesity on quality of life i.e. that patients are severely obese from childhood, should not be under-estimated. Estimates of quality of life taken from the general population can therefore be seen as conservative.

10.1.2 Please describe how patients' health-related quality of life change over the course of the condition

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.

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case.

Health related quality of life was assessed with both general and condition-specific questionnaires during Phase 3 studies. General HRQL measures included the SF-36, SF-10, and PedsQL scales; IWQOL was administered as a condition-specific questionnaire. Whilst mapping to EQ-5D is in theory possible, the small sample size and lack of data collection timing standardisation in the setmelanotide trials meant the resulting data would not be appropriate for cost-effectiveness analysis. The economic model employs a cohort-based Markov (state transition) approach with multiple health states stratified by the BMI/BMI Z-score for both adult and paediatric populations. 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. The data reported in the trials was not sufficiently complete to provide data for

the model and would not have allowed for hyperphagia to be modelled as a separate condition with a separate disutility. Given the mechanism of action of setmelanotide through its impact on hyperphagia, it was felt that hyperphagia should be explicitly modelled.

For these reasons, utility values for the adult population in the model are sourced from EQ-5D utilities from general obesity subjects based on BMI and age. For paediatric subjects, EQ-5D based utilities are informed by the PedsQL score reported in Riazi et al (71) and mapped from Peds QL to EQ-5D based on Khan et al (72). A separate utility for hyperphagia taken from a Rhythm sponsored Vignette study, which intended to identify the value of the utility associated with mild, moderate, and severe hyperphagia, independent of its effects on obesity, is then applied as a multiplier to the BMI or BMI-Z-based health state utilities for both adults and paediatrics, respectively.

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

As QoL data reported in the trials were not suitable for use in the model, no mapping was carried out on these data. However, literature-based paediatric utility scores were mapped from PedsQL to EQ-5D for use in the model. PedsQL scores for the paediatric population were reported by Riazi et al.(71), based on a sample (n=540) of healthy and obese children attending local schools in the UK. These PedsQL scores were then mapped to the EQ-5D scale for the BMI Z-score 0.0-1.0 and 3.5-4.0 groups respectively. The methodology used to derive a mapping from PedsQL to EQ-5D was developed by Khan et al. based on data from a cross-sectional survey conducted in four secondary schools in England amongst children aged 11-15 years. The mapping in the model was based on the two-part logit-Ordinary Least Squares (OLS) regression model 5 (OLS 5) as this reported the smallest errors for the 0.8–1 category of the EQ-5D-Y utility score range,

providing more accurate predictions for the upper end of this measure. The regression equation used to calculate the EQ-5D utilities from PedsQL subscale scores is shown below,

EQ-5D-Y-3L utility score = −0.428496 + 0.009127 * PedsQL Physical Functioning + 0.006611 * PedsQL Emotional Functioning + 0.005705 * PedsQL Social Functioning + 0.006011 * PedsQL School Functioning + 0.000020 * PedsQL Physical Functioning Squared − 0.000048 * PedsQL Emotional Functioning Squared + 0.000011 * PedsQL Social Functioning Squared − 0.000017 * PedsQL School Functioning Squared − 0.000004 * PedsQL Physical Functioning × Emotional Functioning − 0.000055 * PedsQL Physical Functioning × Social Functioning − 0.000066 * PedsQL Physical Functioning × School Functioning − 0.000009 * PedsQL Emotional Functioning × Social Functioning + 0.000059 * PedsQL EmotionalFunctioning × School Functioning − 0.000027 * PedsQL Social Functioning × School Functioning.

Khan et al. validated their regression model by comparing the predicted EQ-5D scores with the observed EQ-5D scores (72). The OLS 5 model was identified to give the best predictions based on a mean squared error of 0.0364 and mean absolute error of 0.1140 amongst the 48 different models that were compared.

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

An SLR was conducted to identify HRQL data using the search methodology and criteria detailed in Section 9.1. Decisions regarding the eligibility of articles for inclusion in the SLRs was based on the population, intervention, comparators, outcomes and study design (PICOS) criteria outlined in Table 63.

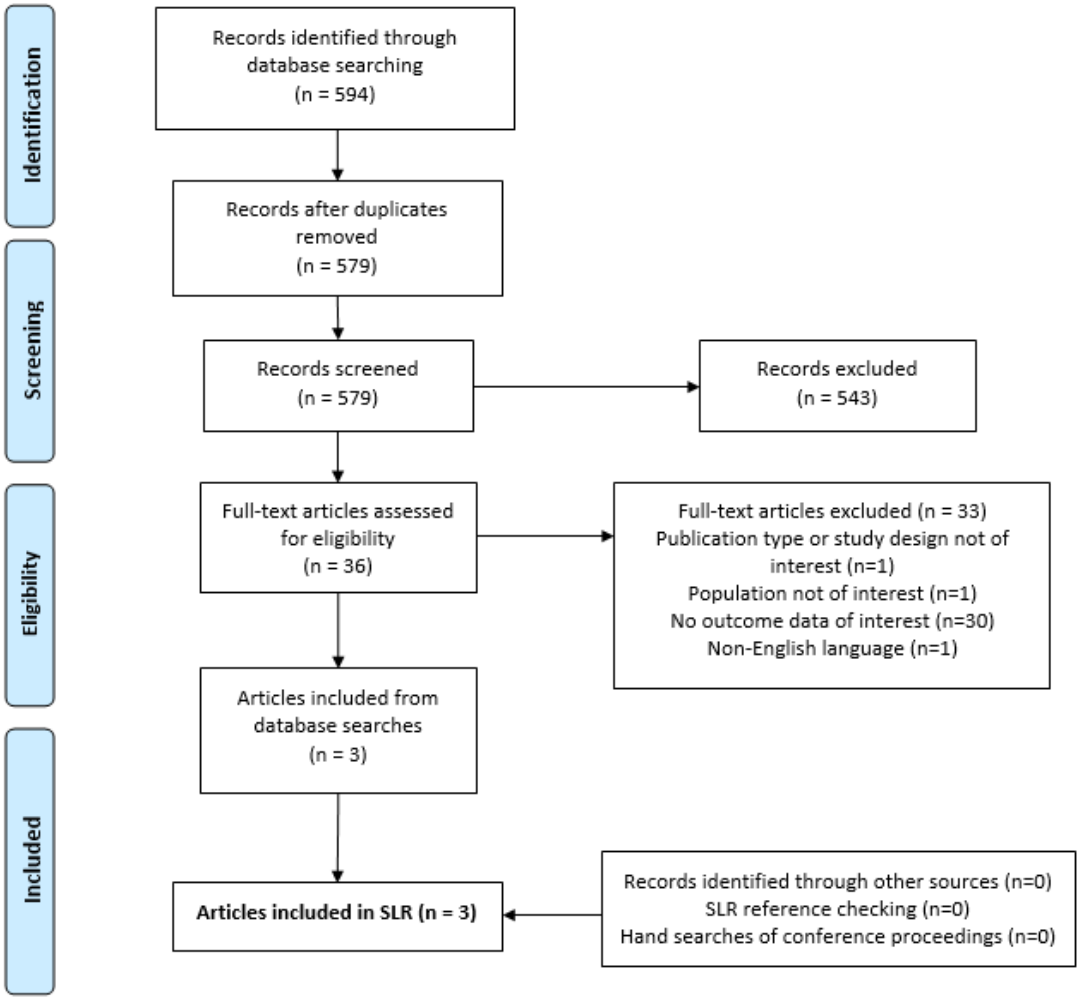
Table 63 Selection criteria for the HRQL SLR

	Inclusion criteria	Exclusion criteria
Population	Paediatric and adult patients with obesity caused by one of the	• Patients aged <6 years

	Inclusion criteria	Exclusion criteria
	following: • LEPR or POMC/PCSK1 deficiency Plus the following obesity markers: • Aged ≥18 years: body mass index (BMI) >30 kg/m^2 • Aged ≥17 years: weight ≥97th percentile for age on growth chart assessment or BMI z-score ≥+2 standard deviation (SD) for children aged 5-19, ≥+3 SD for children aged <5	• Patients with obesity due to other genetic deficiencies or syndromes, or those not meeting age-specific obesity markers • Mixed populations[1] of patients of interest and not of interest for whom the results were not reported separately
Interventions	No restrictions[2]	None
Comparators	No restrictions[2]	None
Outcomes	• Utilities • Disutilities • HRQL • Caregiver burden • Other patient-reported outcomes (PROs)	Studies not reporting any PRO, HRQL, or utility outcome data of interest
Study design	• Clinical trials (single-arm randomised clinical trials) • Observational studies (including case studies and series)	• Letters to the editor, editorials, comments, opinions, notes, narrative reviews • SLR/meta-analyses/network meta-analyses published in 2018 or earlier
Language	English language only	
Search dates		

Systematic search of the literature for HRQL data identified 594 records from electronic databases. After the removal of duplicates, there were 579 unique abstracts eligible for title and abstract screening. Of these, 36 publications were identified for full-text screening. Ultimately, only the three setmelanotide articles met the PICOS criteria. No further data were identified. Figure 21 describes the selection of studies from the initial search to those included.

Figure 21 PRISMA flow diagram of findings from the HRQL SLR



10.1.6 Studies in which HRQL is measured

As no studies were identified in the SLR that provided utility values for the population of interest, utility values have been sourced for the general obesity population. Details of the studies that provide HRQL for the model are provided below:

Study	Riazi et al. (71)	Alsumali et al. (73)	Søltoft et al. (74)	Sullivan et al. (75)
Country	UK	US	UK	US
Sample Size	540 (healthy= 444, obese 96)	37,933	14,416	79,522
Population	Obese and healthy children aged 5-16 years	Adults in 2000-2002 MEPS samples	Individuals aged ≥18 in 2003 Health	Adults in 2000-2003 MEPS samples

			Survey for England	
Intervention	N/A	N/A	N/A	N/A
Elicitation method	PedsQL	EQ-5D	EQ-5D	EQ-5D
Mapping	N/A	N/A	N/A	N/A
Health states	BMI Z-score 0.0-1.0 and 3.5-4.0	See section 10.1.9	Disutilities due to sleep apnoea, osteoarthritis, and type 2 diabetes	Disutilities due to CV events; MI, angina, stroke, and TIA
Utility values	80.3 and 69.7 (PedsQL scale) respectively. 0.89 and 0.82 (EQ-5D scale) respectively	See section 10.1.9	Disutility due to sleep apnoea=0.034, osteoarthritis= 0.187, T2DM=0.043	Disutility due to MI=0.037, angina=0.063, stroke=0.117, TIA=0.033

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Not applicable.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL

Given the limited amount of HRQL data derived from the small patient populations treated in setmelanotide clinical trials, no conclusions relating to the impact of AEs can be made. However, expert opinion was that the main AE, hyperpigmentation, was tolerated by most patients, who as result of their POMC and LEPR deficiencies are generally paler in complexion than the general population at baseline. Pigmentation generally increased initially before plateauing and was evenly distributed across the body.

Nausea and vomiting were generally mild and transient.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case

The cost-effectiveness model includes health states based on BMI for adults and BMI Z-Score for paediatrics. Due to the lack of evidence in published literature for HRQL data in patients with POMC/PCSK1and LEPR deficiency, utility values from patients experiencing general obesity were used in the model. Utility values for adult patients, stratified by BMI and age, are based on the EQ-5D utilities reported in Alsumali et al. derived from 37,933 adults who participated in the 2000-2002 (Medical Expenditure Panel Survey) MEPS (73). Paediatric utility values based on BMI Z-score are based on PedsQL utility values mapped to EQ-5D utilities based on the methodology published by Khan et al (72). These utility values are expected to be conservative representations of HRQL in patients with POMC/PCSK1 and LEPR deficiency as clinical experts have indicated these conditions are substantially more severe than general obesity. They are derived from the most relevant surrogate indication and therefore the most appropriate for use in the model given the lack of evidence for the populations of interest.

The impact of hyperphagia on HRQL in the model is informed based on the vignette study conducted by Rhythm Pharmaceuticals which quantified the utility due to mild, moderate, or severe hyperphagia alone. HRQL of obesity-related complications is included in the model based on the EQ-5D disutility values reported in Søltoft et al. and Sullivan et al. based on surveys of general population adults in UK and USA respectively. While the EQ-5D utility scores reported in the catalogue developed by Sullivan et al. are based on US community preferences and not on the UK community preferences, these utility scores are widely used in cost-effectiveness models submitted to NICE as it meets many of NICE's requirements for preference-based HRQL scores (75).

Any remaining data gaps were filled from other published sources or assumptions as outlined. The table below specifies all utility values used in the cost-effectiveness model along with their respective justifications.

Table 64 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
BMI 20-25, age 18-30	0.91	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 31-40	0.89	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 41-50	0.86	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 51-60	0.83	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 61-70	0.81	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 71-80	0.79	-	Alsumali et al. 2018(73)	See section 10.3
BMI 20-25, age 81+	0.79	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 18-30	0.91	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 31-40	0.89	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 41-50	0.86	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 51-60	0.83	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 61-70	0.81	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 71-80	0.79	-	Alsumali et al. 2018(73)	See section 10.3
BMI 25-30, age 81+	0.79	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 18-30	0.89	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 31-40	0.86	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 41-50	0.82	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 51-60	0.8	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 61-70	0.79	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 71-80	0.76	-	Alsumali et al. 2018(73)	See section 10.3
BMI 30-35, age 81+	0.76	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 18-30	0.88	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 31-40	0.83	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 41-50	0.79	-	Alsumali et al. 2018(73)	See section 10.3

BMI 35-40, age 51-60	0.77	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 61-70	0.76	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 71-80	0.74	-	Alsumali et al. 2018(73)	See section 10.3
BMI 35-40, age 81+	0.74	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 18-30	0.84	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 31-40	0.82	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 41-50	0.75	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 51-60	0.73	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 61-70	0.71	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 71-80	0.69	-	Alsumali et al. 2018(73)	See section 10.3
BMI 40-45, age 81+	0.69	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 18-30	0.84	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 31-40	0.82	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 41-50	0.75	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 51-60	0.73	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 61-70	0.71	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 71-80	0.69	-	Alsumali et al. 2018(73)	See section 10.3
BMI 45-50, age 81+	0.69	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 18-30	0.8	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 31-40	0.77	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 41-50	0.7	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 51-60	0.69	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 61-70	0.66	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 71-80	0.66	-	Alsumali et al. 2018(73)	See section 10.3
BMI >50, age 81+	0.66	-	Alsumali et al. 2018(73)	See section 10.3
BMI Z-Score 0.0-1.0	0.89	-	Riazi et al., 2010(71). Mapped PedsQoL to	See section 10.3

			EQ-5D based on Khan et al. 2014(72)	
BMI Z-Score 1.0-2.0	0.87	-	Linear extrapolation	See section 10.3
BMI Z-Score 2.0-2.5	0.86	-	Linear extrapolation	See section 10.3
BMI Z-Score 2.5-3.0	0.85	-	Linear extrapolation	See section 10.3
BMI Z-Score 3.0-3.5	0.83	-	Linear extrapolation	See section 10.3
BMI Z-Score 3.5-4.0	0.82	-	Riazi et al., 2010(71). Mapped PedsQL to EQ-5D based on Khan et al. 2014(72)	See section 10.3
BMI Z-Score ≥4.0	0.81	-	Linear extrapolation	See section 10.3
Mild hyperphagia	[redacted]	-	Vignette study(2)	No published evidence available for utility associated with hyperphagia alone
Moderate hyperphagia	[redacted]	-	Vignette study(2)	No published evidence available for utility associated with hyperphagia alone
Severe hyperphagia	[redacted]	-	Vignette study(2)	No published evidence available for utility associated with hyperphagia alone
Disutility due to sleep apnoea	0.034	-	Søltoft et al. (2009)(74)	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
Disutility due to osteoarthritis	0.187	-	Søltoft et al. (2009) (74)	Based on association between musculoskeletal problems and HRQL. Average of utility decrements by sex were used

Disutility due to NAFLD	0.000	-	No evidence available.	No added disutility assumed. Assumption based on the suggestion NAFLD GDG (Guideline Development Group)(76) to consider utility for NAFLD similar to patients with obesity
Disutility due to T2DM	0.043	-	Søltoft et al. (2009) (74)	Based on association between type 2 diabetes and HRQL. Average of utility decrements by sex were used
Disutility due to CV events	0.064	-	Sullivan et al. (2011)(75)	Weighted average of HRQoL decrements based on the CV event type and proportion of each CV event type

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were not consulted for the estimation of utility values used in the model. All utility/disutility values used in the model are based on evidence found in literature.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL.

Health states are defined as BMI ranges with a five-point spread (e.g., 30-35, 35-40, etc.) or BMI-Z ranges with a 0.5 point spread (e.g. 3.0-3.5, 3.5-4.0 etc). Each BMI or BMI-Z health state is associated with a constant utility value based on evidence from the literature, however note that these spreads correspond to values that are greater than the MCID, patients do not therefore need to move to a new BMI range to experience clinically meaningful improvements. Variation of utility score within each health state due to hyperphagia and/or comorbidities of obesity are accounted for by applying a separate utility score to each BMI or BMI-Z health state based on hyperphagia status (mild, moderate, or severe), as well as disutility scores related to specific comorbidities, respectively.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Disutility due to AEs was excluded from the analysis as the incidence of AEs requiring management is negligible in the clinical trials of setmelanotide. In addition, disutility scores due to some potential comorbidities of obesity (e.g., breast and gastorintestinal cancer), were excluded from the analysis based on clinical expert opinion, which suggested prioritising the comorbidities that were included in the analysis based on the greatest relevance to the populations of interest

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life for the participants considered in the analysis is based on the health state-based utilities found in literature and the individual participant's hyperphagia status (see Section 10.9). A quality of life multiplier

is used to realize the impact of hyperphagia experienced by the participants. Additionally, quality of life decrements are applied to these resultant utility values and depend upon the number of comorbidities experienced by the participant.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is not expected to be constant over time and changes based on the individual participant's age and BMI. Additionally, HRQL is also affected by the participant's hyperphagia status and the presence of comorbidities which incur a quality of life decrement based on the number and type of comorbidities experienced by the participant. Additional details about this quality of life estimates, multiplier, and decrements are provided in section 10.9

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Quality of life estimates for the health states based on BMI Z-Scores are derived from Riazi et al., 2010 which reports utilities based on the PedsQoL scale (71). As all other health related quality of life estimates used in the model are based on the EQ-5D instrument, these PedsQoL estimates are transformed to EQ-5D based estimates based on the mapping of PedsQoL to EQ-5D published in Khan et al. 2014 (72)

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional

treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

During the clinical trials participants were assessed for response at 12 weeks/3 months after initiating treatment and those not responding to treatment were discontinued. Response to treatment was defined as loss of at least 5kg reduction in body weight or ≥5%weight loss. The same continuation rule has been applied in the economic model, that is, participants not responding to treatment discontinued treatment after 12 weeks, while the participants responding to treatment continued to be on treatment until death. This stopping rule will identify patients who are most likely to benefit from setmelanotide based on measures (weight) that are routinely assessed in UK practice. By ensuring only patients who are benefitting from setmelanotide treatment, this rule is likely to predict those patients for whom the technology constitutes particular value for money.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in Appendix 3.

Details of the economic evidence SLR capturing health economic data and studies relevant to the decision problem are provided in Appendix 3.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature.

The inclusion and exclusion criteria used in the economic evidence SLR are outlined in Appendix 3.

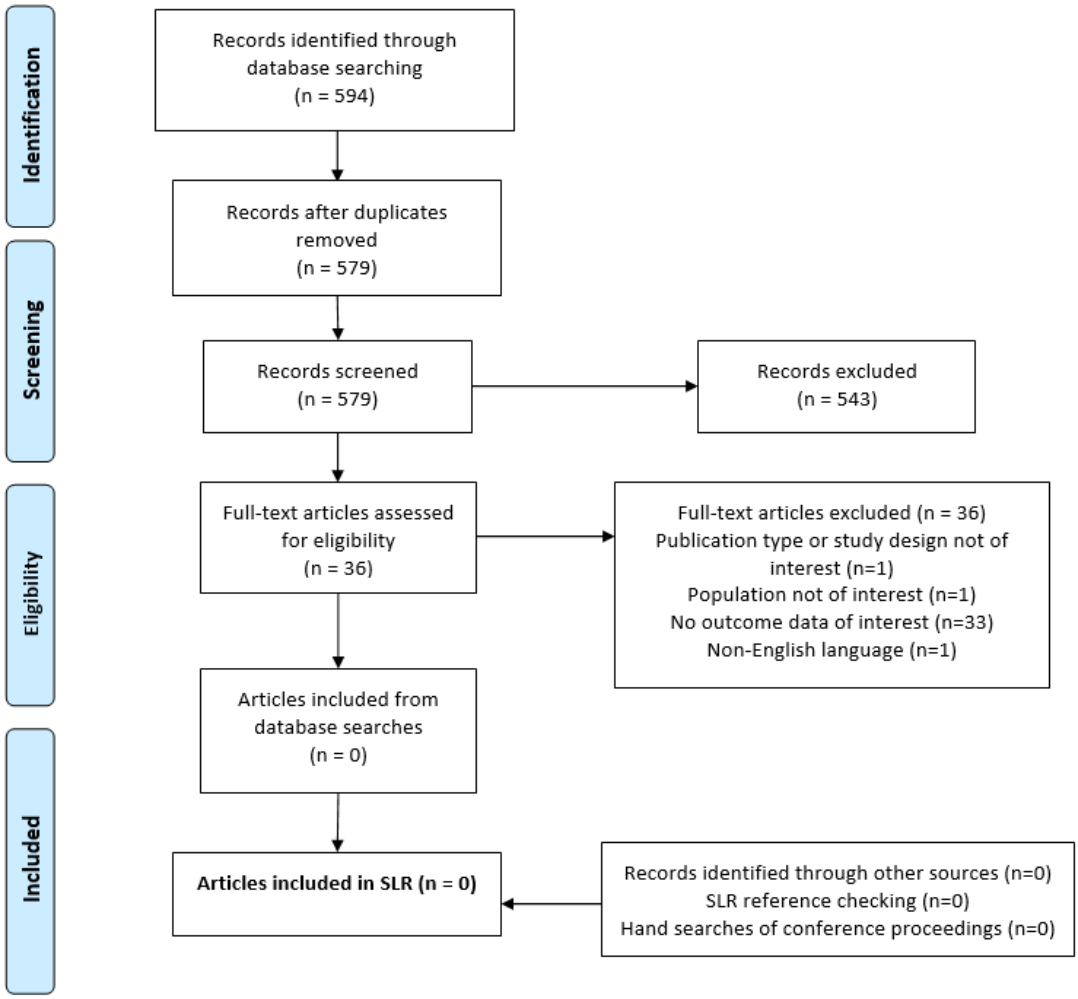
11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Searches for relevant evidence yielded 594 records from electronic literature databases. After the removal of duplicates, there were 579 unique abstracts eligible for title and abstract screening. Of these, 36 publications were identified for full-text screening. None of the studies identified through database searches were deemed to meet the criteria for inclusion in the economic burden SLR. Furthermore, no relevant studies were identified through grey literature sources.

Hence, no evidence on the economic burden of disease or the cost-effectiveness of interventions for the treatment of obesity caused by PPL or

LEPR mutations was identified. presents the selection of studies from the initial search hits to the final number of included studies as shown in Figure 22.

Figure 22 PRISMA Diagram



Abbreviation: SLR = systematic literature review

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

No evidence on the economic burden of disease or the cost-effectiveness of interventions for the treatment of obesity caused by PPL or LEPR mutations was identified during the SLR. A hand search of previously developed CEMs used in obesity-related NICE submissions was performed to determine if relevant information was available to potentially inform the structure for the setmelanotide model. Specific submissions identified are noted below:

The most recent model (TA664) utilised a state-transition, Markov, cohort approach to model the changes in BMI trajectories of individuals being treated with liraglutide (82). The current BMI of the individuals also affected the risks of developing obesity-related comorbidities such as T2DM, cardiovascular (CV) events, sleep apnoea, and cancer. The submission for naltrexone–bupropion for managing patients who were overweight and obese (TA494) used an individual, patient-level simulation approach using a discretely integrated condition-event methodology implemented in Excel® (83). The rimonabant (TA144) submission utilised both a cohort, Markov model structure and a patient-level approach using discrete-event simulation (84). Lastly, the metreleptin submission (HST14) submitted two models: an individual patient-level simulation approach and the subsequent partitioned survival approach that focused purely on mortality (85).

11.2.2 Provide a complete quality assessment for each health economic study identified.

No evidence on the economic burden of disease or the cost-effectiveness of interventions for the treatment of obesity caused by LEPR or POMC mutations was identified.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The scope of the analysis considered in the cost-effectiveness model (CEM) analyses was aligned with the licensed indication for setmelanotide: treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic LEPR or POMC (including PCSK1) deficiency in adults and children aged six years old and above.

The baseline characteristics of patients with LEPR and POMC/PCSK1 deficiencies relevant to the economic model are summarised in Table 65. These are based on the complete cohorts (i.e., pivotal and supplemental) from the two single-arm, open-label, multicentre, phase III trials: POMC/PCKS1 trial (NCT02896192) and LEPR trial (NCT03287960), which included individuals aged six years or older with obesity caused by a LEPR or POMC/PCSK1 deficiency, respectively.

Table 65 Baseline Characteristics

	POMC/PCSK1 deficiency (n=15)	LEPR deficiency (N=15)
Age, years	17.2 (7.02; 7.0 – 30·0)	21.67 (8.52; 8.0 – 37.0)
Sex, N	9 males (60.0%) 6 females (40.0%)	6 males (40.0%) 9 females (60.0%)
BMI, kg/m²	39.17 (8.21; 26.6 – 53.3)	49.21 (13.02; 28.1 – 69.7)
Average hunger score	6.7 (0.7; 6.0 – 8.0)	5.7 (1.03; 4.0 – 8.0)

Abbreviations: BMI = body mass index; LEPR = leptin receptor; PCSK1 = pro-protein convertase subtilisin/kexin type 1; POMC = pro-opiomelanocortin

Data are mean (standard deviation; range) and n (%).

*Reported BMI in NCT02896192/NCT03287960 includes paediatric subjects, for whom BMI-Z score is more appropriate. The reported range therefore does not reflect the BMI range used for adults in the model.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The comparator for the analysis is best supportive care (BSC). In the UK, the BSC for patients with obesity due to genetic mutations defaults to general obesity care, which includes the use of lifestyle and dietary interventions as well as behavioural therapy (as per the NICE guideline CG189 (77)). The introduction of setmelanotide in England is not expected to displace or reduce BSC in treating obesity in patients with genetic LEPR or POMC/PCSK1 deficiencies; it is expected to improve the impact of these interventions after an initial weight-loss period that resulted from sustained treatment with setmelanotide.

Other comparators previously included in the scope - such as orlistat, methylcellulose, and bariatric surgery - are not routinely used or effective in real-world clinical practice in individuals with obesity associated with LEPR and POMC/PCSK1 deficiencies, according to discussions with Professor Sadaf Farooqi, a UK-based clinical expert in the treatment of such patients (8). Furthermore, there is little evidence published on the use of these treatments in such patients, and those publications that have reported such data showed the general ineffectiveness of these treatments. Individuals who underwent treatment with methylphenidate (methylcellulose base) experienced no impact on their weight or reduction in their underlying hyperphagia (78). Based on expert opinion from clinicians, methylcellulose is

not commonly used in practice to treat patients with POMC/PCSK1 and LEPR deficiencies (8). For bariatric surgery, post-procedure weight loss is mainly dependent on mechanical restriction, and there is no additional effect on neurohormonal appetite regulation (79). Therefore, patients with LEPR or POMC/PCSK1 or deficiency would not be expected to experience a decrease in appetite following bariatric surgery, as the treatment does not directly affect the hormonal axis responsible for obesity. As a result, the majority of patients with LEPR and POMC/PCSK1 deficiencies who underwent bariatric surgeries regained weight following the procedure due to persisting hyperphagia (80). Finally, there is no published evidence on the use of orlistat in these populations. Based on previous discussions with UK clinical experts (8), orlistat is not used in these population in clinical practice. Hence, neither methylcellulose, nor orlistat, nor bariatric surgery were deemed appropriate to be included in the analyses as a comparator.

Due to these reasons, according to clinical experts only BSC, which includes diet advice and lifestyle management, is provided to patients with LEPR and POMC/PCSK1 deficiency and is the only comparator included in the economic model. However, this treatment regimen ultimately proves to be ineffective in such patients as it does not affect the defective MC4R axis and, in turn, is not expected address the underlying hyperphagia that is primarily responsible for severe obesity.

Model structure

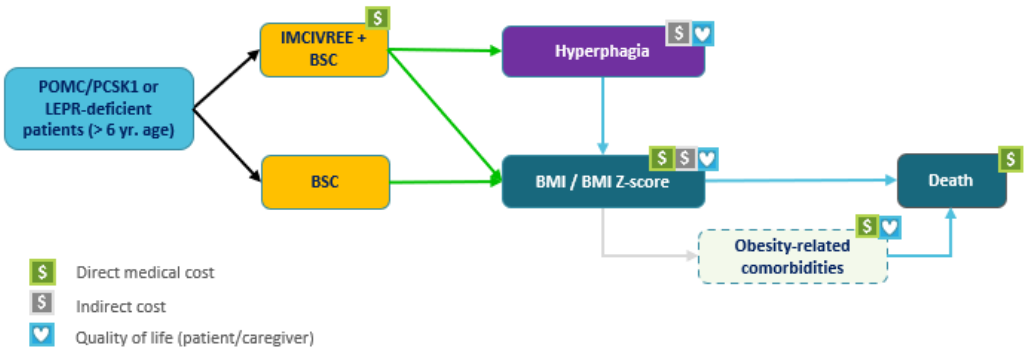
12.1.3 Provide a diagram of the model structure you have chosen.

To evaluate the cost-effectiveness of setmelanotide in treating obesity due to LEPR and POMC/PCSK1 deficiencies, a novel CEM was developed. It employs a cohort-based Markov (state-transition) approach with multiple health states stratified by the BMI/BMI Z-score for both adult and paediatric populations, as well as a death state. Furthermore, the model tracks medical resource utilisation (MRU) costs for the treatment of obesity, accounts for the utility associated with hyperphagia, and accrues the costs and disutilities associated with the most relevant obesity-related complications in this patient population (including sleep apnoea, osteoarthritis, non-alcoholic fatty liver

disease [NAFLD], type 2 diabetes mellitus [T2DM], and cardiovascular disease [CVD]).

A high-level overview of the model structure is shown in Figure 23. Eligible patients in the model are treated with either BSC or a combination of setmelanotide and BSC. Markov health states in the model are BMI/BMI-Z and death. Treatments can affect both BMI/BMI-Z (inducing either weight loss, maintenance, or regain), and hyperphagia, which is not modelled as separate set of health states but treated as a condition within each BMI/BMI-Z health state and assigned a separate utility corresponding to severity (mild, moderate, or severe). Changes in BMI over time in the model lead to changes in obesity-related comorbidities, which are also tracked as conditions within each BMI health state, and incur both treatment costs and a disutility, and increased risk of mortality. Patients from any BMI health state can move to the death state as a consequence of complications from comorbidities of obesity in addition to other common conditions such as infections and immunodeficiency.

Figure 23 High-level Model Diagram



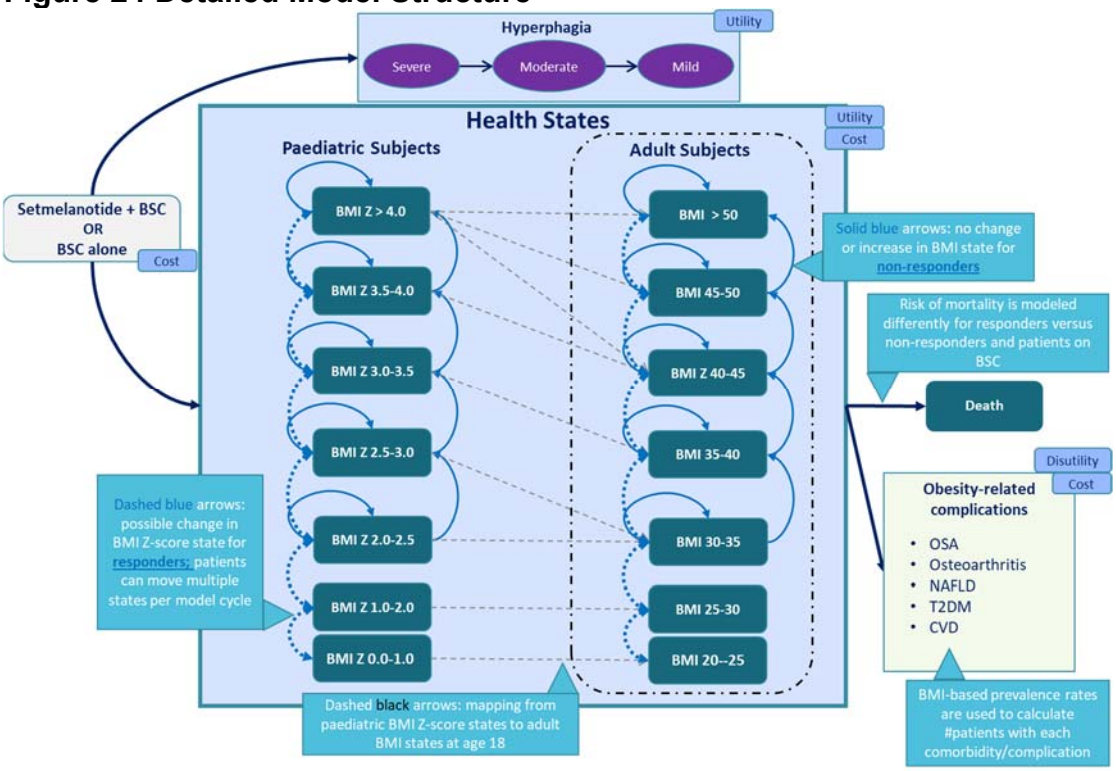
Additional details related to the modelling of BMI health states is shown in Figure 24. The model accounts for seven different categories of BMIs (adults) and BMI Z-scores (paediatrics), as well as the risk of death from any BMI or BMI Z-score. Adult BMI categories are aligned with NICE guidelines, with additional high BMI classes (> 40) to accommodate patients with LEPR deficiencies. The BMI Z-score state for paediatric patients who transition to adulthood (i.e., 18 years) is mapped to the corresponding adult BMI state, as

depicted via black arrows in Figure 24. The proportion of patients in the highest paediatric BMI Z health state (4.0) is equally distributed across the adult BMI ≥40 health states (i.e., BMI 40–45, 45–50, and >50).

LEPR and POMC/PCSK1-deficient patients entering the model are expected to experience hyperphagia and can experience a change in both BMI and hyperphagia severity as a result of being treated with setmelanotide or BSC. Both changes will impact quality of life and utilities are therefore modelled separately, although of the two, only BMI is modelled as a Markov state. Additionally, subjects entering the model can have a combination of obesity-related comorbidities, each of which includes a corresponding disutility score. The rate at which these comorbidities increase/decrease as a consequence of treatment is directly tied to BMI changes in the model and can result in either increased prevalence or remission of these comorbidities.

The risk of mortality in the model for untreated patients is modelled based on average life expectancy of patients with LEPR or POMC/PCSK1 deficiency as informed by a UK clinical expert (8). However, the risk of mortality in patients treated with setmelanotide is dependent upon by the BMI / BMI Z-score health state and age for the general obesity population which considers the impact of comorbidities of obesity. This approach to modelling the treatment effect (i.e., primarily through an impact on survival) is based on the input of a UK clinical expert indicating that treatment of patients with POMC/PCSK1 deficiency with setmelanotide will alter their disease trajectory in such a way that they more resemble patients with general obesity of approximately equivalent BMI or BMI-Z if they respond to treatment (8).

Figure 24 Detailed Model Structure



Abbreviations: BMI = body mass index; BSC = best supportive care; CVD = cardiovascular disease; KOL = key opinion leader; NAFLD = non-alcoholic fatty liver disease; T2DM = type 2 diabetes mellitus. Colour codes: turquoise = health state with associated cost and utility; purple = condition associated with each BMI health state, with separate utility score; yellow = condition associated with each BMI health state with associated disutility and cost.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

Obesity associated with LEPR and POMC/PCSK1 deficiency is chronic. Patients diagnosed with these RGDOs experience hyperphagia (81) due to impaired MC4R pathway functioning, which is characterised by an overwhelming, heightened, and relentless hunger (with a primary consequence of excessive energy intake) (2). The impacts of obesity from these monogenic conditions can include premature mortality (often in very young patients with LEPR deficiencies, resulting from infections and respiratory disorders) and severe impact on QoL due to hyperphagia and various complications related to extreme BMI (e.g., obstructive sleep apnoea, osteoarthritis and musculoskeletal pain, NAFLD, and T2DM). These conditions have the potential to have a cumulative effect on patients' QoL, can be present from a very early age, and persist throughout the patients' lifetime.

Prior obesity treatment models specific to the general obesity population may be of limited relevance since no approved treatment is currently available for

subjects with these monogenic disorders. However, a hand search of previously developed CEMs used in obesity-related NICE submissions was performed to determine if relevant information was available to potentially inform the structure for the setmelanotide model. Specific submissions identified are noted below:

The most recent model (TA664) utilised a state-transition, Markov, cohort approach to model the changes in BMI trajectories of individuals being treated with liraglutide (82). The current BMI of the individuals also affected the risks of developing obesity-related comorbidities such as T2DM, cardiovascular (CV) events, sleep apnoea, and cancer. The submission for naltrexone–bupropion for managing patients who were overweight and obese (TA494) used an individual, patient-level simulation approach using a discretely integrated condition-event methodology implemented in Excel® (83). The rimonabant (TA144) submission utilised both a cohort, Markov model structure and a patient-level approach using discrete-event simulation (84). Lastly, the metreleptin submission (HST14) submitted two models: an individual patient-level simulation approach and the subsequent partitioned survival approach that focused purely on mortality (85).

The setmelanotide model structure shown above aligns generally with the key features of the model structures used in previous obesity submissions, including the representation of BMI and inclusion of relevant comorbidities. It is important that it accounts explicitly for key elements relevant to subjects with LEPR and POMC/PCSK1 deficiencies not reflected in the prior submission models:

- A representation of very high BMI and BMI Z-score states reflective of morbid obesity (BMI >40 and BMI Z-score >3.5), which was observed in these subjects clinically.
- Explicit accounting of the utility related to hyperphagia (which is a feature unique to diseases related to the MCR4 axis (see Hyperphagia below).

- The impact of long-term chronic weight management (BMI or BMI Z-score reductions) on overall survival, key comorbidities of obesity, and cost and disutility implications (see Comorbidities below).

Despite the known impact of baseline patient characteristics on the complications of obesity, a Markov cohort structure was chosen rather than an individual simulation. This was due in part to a paucity of evidence available to relate the baseline characteristics of patients with LEPR and POMC deficiency to long-term outcomes, and also in part to the lack of similarity between these subjects and the general obesity population when untreated. Therefore, the use of general obesity literature as a surrogate indication to procure the data necessary to develop an individual simulation was not warranted.

12.1.4.1 ***Hyperphagia***

POMC neurons and LEPR (located on POMC neurons) are both associated with MC4R in the melanocortin pathway, and reduced activity in this pathway results in hyperphagia. Hyperphagia is characterised by an overwhelming, heightened, and relentless hunger; a longer amount of time needed to reach and a shorter duration of satiety; severe preoccupation with food; persistent and potentially extreme food-seeking behaviours (such as night eating, stealing food, and eating non-food items); and distress or inappropriate behavioural responses if denied food. It has a considerable impact on the individual's QoL, which is not well captured by existing utility measures. Therefore, an independent hyperphagia-based utility multiplier derived from a company-sponsored vignette study (2) was applied to the age- and BMI-based utility scores assigned to each BMI health state.

For the model, the baseline hyperphagia severity distribution in patients (mild, moderate or severe) was based on an assumption derived from the opinion of a UK clinical expert (8), who noted that the majority of LEPR and POMC/PCSK1-deficient patients exhibit moderate to severe hyperphagia, with the condition tending towards greater severity in LEPR subjects. However, as there was no opinion available on the reduction of hyperphagia in these patients after administration of setmelanotide, the average hunger scores reported in the trial were used as a basis for mapping to hyperphagia severity.

A hunger score of ≥7 (on a scale of 1-10) was considered to correspond to severe hyperphagia, a hunger score of 4-6 was considered to correspond to moderate hyperphagia, and a score of ≤4 was considered to correspond to mild hyperphagia based on discussion with the clinicians who were consulted in the design of the vignette study who had experience treating patients with hyperphagia (2). It should be noted that this approach likely under-represents the utility decrement due to hyperphagia, as the hunger score alone does not fully represent the impact of hyperphagia on an individual according to the opinion of clinical experts (2). This approach is therefore likely a conservative assumption.

The approach outlined above was chosen in lieu of the approach chosen in the metreleptin submission (HST14) (85). The latter methodology was criticized by the NICE ERG for underestimating the true impact of hyperphagia on an individual's quality of life. The use of an independent utility multiplier connected to hyperphagia directly addresses this prior concern, although it requires clinician-validated assumptions for the choice of mapping between average hunger score and hyperphagia. However, given the paucity of the data available to directly characterize hyperphagia outside of the company-sponsored vignette study (2), although imperfect, it was considered the most credible approach available.

12.1.4.2 ***Comorbidities***

Based on Prof. Farooqi's opinion, the model is designed to consider the following major comorbidities attributable to excess weight due to obesity: obstructive sleep apnoea, osteoarthritis, NAFLD, T2DM, and CV events. Due to data gaps in the population of interest, the prevalence of comorbidities stratified by age and BMI is informed by the opinion of clinical experts, published literature for general obesity subjects, and assumptions (Section Prevalence of Comorbidities). Of note there are other co-morbidities associated with excess weight which lower the QoL of patients. However, they were not taken into consideration in the model due to lack of data for these specific patient populations (LEPR and POMC deficiency). Therefore, this cost-effectiveness model can be considered a very conservative estimate for the condition of interest.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

All model assumptions and their justification are shown in Table 66.

Table 66 Model Assumptions

Assumption	Justification
Survival	
In terms of their lifespan and mortality risk, responders to setmelanotide will follow a disease trajectory that is similar to general obesity patients. The life expectancy of responders is modelled based on a set of hazard ratios (HRs) stratified by BMI level from general obesity literature. An option for a user-specified multiplier on the HRs is provided to reflect a potential higher mortality risk for POMC/PCSK1 and LEPR-deficient patients and set higher for the latter patients in the base case.	The phenotype of responders changes and more resembles a general obesity patient when they are responding to setmelanotide due to reductions in hyperphagia, according to clinical expert opinion (8). Considering the severity of complications in patients with LEPR and POMC deficiency patients, responder patients, especially those with LEPR-deficiency, are likely to have worse survival than general obesity population based on clinical expert opinion (8).
The life expectancy of non-responders to setmelanotide or POMC/PCSK1/ LEPR-deficient patients on BSC is modelled using survival distributions, in which the parameters are informed based on inputs from clinical experts.	Systematic literature reviews found no data characterizing the average lifespan of patients with these diseases. Survival data from general obesity population literature was deemed to be a poor proxy due to the different root causes of disease, so the input of a clinical expert (8) was used to inform the parameters of the survival distributions. Interviews with clinical experts suggested that LEPR/POMC deficient patients have a shorter lifespan compared to general obesity population mainly due to early onset of obesity and accelerated incidence of comorbidities, including infections, immunodeficiency, and respiratory issues.
Risk of all-cause mortality is modelled independently of the incidence of obesity-related comorbidities	Cause-specific mortality was not considered as LEPR/POMC deficient patients usually experience multiple comorbidities (2). Use of independent sources could potentially result in double-counting the risk.
Hyperphagia	
The baseline hyperphagia severity distribution in patients (mild, moderate or severe) was assumed to include a mix of moderate and severe hyperphagia.	No data are available to characterize hyperphagia severity in the patient populations of interest; the opinion of a clinical expert (8) was used to inform the distribution.

Hunger score one-year post-treatment is mapped to hyperphagia. The observed effect of treatment with setmelanotide on hyperphagia during the clinical trials is applied at the beginning of the first cycle for responders and persists throughout the patients' lifetime.	No data specific to hyperphagia were available from the clinical trials. One-year data on hunger score was available from the trials (86, 87) and used as a surrogate despite the understanding that this use of the evidence likely under-represents the severity of hyperphagia (2) and is therefore a conservative assumption. As the underlying mechanistic defect is treated by setmelanotide, the effect of treatment on hyperphagia is assumed to be maintained after one year for responders as suggested by a clinical expert (8).
Paediatric model	
Paediatrics are modelled using the same essential structure as for adults, but BMI Z-score is used to define health states instead of BMI. Paediatrics' BMI z-score state is mapped to a corresponding adult BMI state after the patient grows into adulthood (i.e., after age 18).	BMI Z-score is a more commonly accepted standard for characterizing obesity in paediatric patients (88).
Cost	
Administration cost for setmelanotide is not included in the model	Setmelanotide is self-administered
Non-responders accrue 3 months of treatment cost	Per NICE treatment guidelines (77) and as captured in the setmelanotide trials where response to treatment was assessed at 3 months. Non-responders were defined as patients who do not achieve a >5% weight loss at the end of three months (55) and did not receive treatment after this timepoint in the trial.
The mean annual comorbidity cost is considered to accumulate the cost of comorbidities	Based on clinical expert opinion (8)
Weight loss, maintenance or regain	
LEPR and POMC/PCSK1 deficient patients experience BMI gain as paediatrics, but their BMI does not change substantially after reaching adulthood. No change in BMI Z-score is considered during paediatric age as natural weight gain does not impact BMI Z-score level.	Based on clinical expert opinion (89)
After the trial duration, the effect of setmelanotide on BMI reduction is maintained until subjects reach borderline obesity for POMC/PCSK1 patients and achieved BMI level is	Based on clinical expert opinion (8)

maintained for LEPR patients. The flexibility to change BMI state at a certain level after a certain duration is built into the model.	
The paediatric and adult health states are not further stratified above BMI Z-score of 4.0 and BMI of 50.	There is limited data in the literature on patients in these severely obese subjects and any input data for such states would have been based on pure assumption or extrapolation from general obesity subjects
Comorbidity	
Prevalence rates for modelled comorbidities are informed based on literature on morbidly obese patients who were eligible or considered weight loss surgery. Corresponding prevalence rates are applied to the number of patients in each BMI class in each cycle to determine the total number of patients with different comorbidities.	No evidence was found in the systematic literature review to characterize the prevalence rate of comorbidities in POMC/PCSK1 and LEPR deficient patients. Prevalence rates from morbidly obese patients who were eligible or considered for weight loss surgery were the closest proxy for these patients.
Prevalence rates for modelled comorbidities vary by BMI; the same rates are applied for adults and paediatrics.	No evidence was found in the systematic literature review to stratify the prevalence of modelled comorbidities by both BMI and age.
CVD and T2DM are only considered in adults and cancer is not considered.	CVD and T2DM are not key risk factors for paediatric patients and most untreated LEPR and POMC/PCSK1 deficient patients die before they can develop cancer based on clinical expert opinion (8).
Utility	
Utility estimates for different hyperphagia status are informed from a vignette study and applied to age/BMI specific patient utility values in a multiplicative fashion (2).	Use of a multiplicative approach to derive an aggregated health state utility from multiple utilities based on independent factors/conditions is based on established methodology (8)
Limitations	
Patients' hyperphagia status is updated for responders to setmelanotide treatment. The distribution of hyperphagia status pre-/post-treatment is independent of patients' BMI health states.	Capturing such detail requires expanding the number of health states by a factor of three (i.e. inclusion of health states for mild, moderate, severe hyperphagia rather than tracking as a condition within each health state as done here) and significantly more patient level data that is not available.

Abbreviations: BMI = body mass index; BSC = best supportive care; CV = cardiovascular; CVD = cardiovascular disease; HR = hazard ratio; KOL = key opinion leader; LEPR = leptin receptor; NICE = National Institute for Health and Care Excellence; PCSK1 = pro-protein convertase subtilisin/kexin type 1; POMC = pro-opiomelanocortin; T2DM = type 2 diabetes mellitus; WHO = World Health Organization

12.1.6 Define what the model's health states are intended to capture.

In the selected modelling approach, the adult health states are BMI categories with increments of five points each that generally align with NICE guidelines;

additional BMI states are included for extremely high BMIs to accommodate patients with LEPR deficiency. For paediatric patients, health states are defined by the BMI Z-score to align with commonly used obesity definitions.

When the paediatric patients reach adulthood, the BMI Z-score-based health states are mapped to BMI-based health states using calculations published by WHO based on UK statistics (90).

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table 67.

Table 67 Other Key Features in the Model

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	NICE recommends a time horizon that reflects the differences between costs and outcomes between alternative technologies. The base-case model time horizon is a lifetime to reflect the life-long nature of POMC/PCSK1 and LEPR-deficiency, allowing full costs and benefits over the survival time of all patients modelled to be captured.	NICE HST Guidance (91)
Discount	3.5% for costs and 1.5% for health benefits	NICE accepts a non-reference case discount rate of 1.5% for costs and health effects when the 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 at least 30 years). As seen in the results of the base-case and sensitivity analyses, setmelanotide extends the average life expectancy of these patients by a considerable level in virtually all cases and that the benefits of setmelanotide treatment are realised for the patient's full life span. Furthermore, a differential discount rate has been previously used and accepted by NICE (mifamurtide submission, TA235).(National Institute for Health and Care Excellence 2011) The cost-effectiveness estimates in that appraisal were sensitive to the discount rate used; the committee was provided with a clarification note for considering using the discount rates of 3.5% for costs and 1.5% for health effects the in sensitivity analyses, as the treatment effects were both substantial and sustained over a very long period (at least 30 years)	(92) NICE TA235 (93) Ara and Brazier, Value Health 2010 (94)
Perspective (NHS/PSS)	UK NHS perspective		(93)

Cycle length	One year	The cycle length aligns with the literature to capture long-term disease progression and is consistent with the follow-up periods reported in the pivotal clinical trials of setmelanotide	Based on clinical trials (NCT03287960)(86) (NCT02896192)(55, 87)
Average dose on treatment	Trial period- 2.2 mg/day Post-trial= 1.8mg/day	Patients enrolled in the in the clinical trials (86, 87) were on an average dose of 2.2 mg/day at the beginning of the trials. At the end of trial period, these patients were observed to be on an average dose of 1.8 mg/day	
NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

12.2.1.1 *Clinical Inputs*

The distribution of patients amongst adult and paediatric subjects as well as the distribution of individuals with LEPR vs. POMC/PCSK1 deficiencies was informed by the baseline cohort characteristics from the LEPR (NCT03287960) and POMC/PCSK1 (NCT02896192) trials. Additionally, data from the clinical trials (86, 87) was used to inform the baseline cohort demographics, the starting distribution of patients in the BMI-based health states, and the baseline distribution of hyperphagia severity.

12.2.1.2 *Treatment Dose*

The model accounts for dose titration based on the average therapeutic dose observed in the clinical trials (86, 87). As a result, POMC/PCSK1 and LEPR deficient patients are expected to be on an average dose of 2.2 mg/day during their first year on treatment. After the first year on treatment, this dose is titrated down to 1.8 mg/day based on the average therapeutic dose observed at the end of trial period for patients enrolled in the clinical trials (86, 87). The reduced dose is then maintained in patients who continue on treatment until death to represent a treatment maintenance phase, in accordance with the opinion of a clinical expert who indicated further dose titration in patients who respond would likely not occur in clinical practise (8).

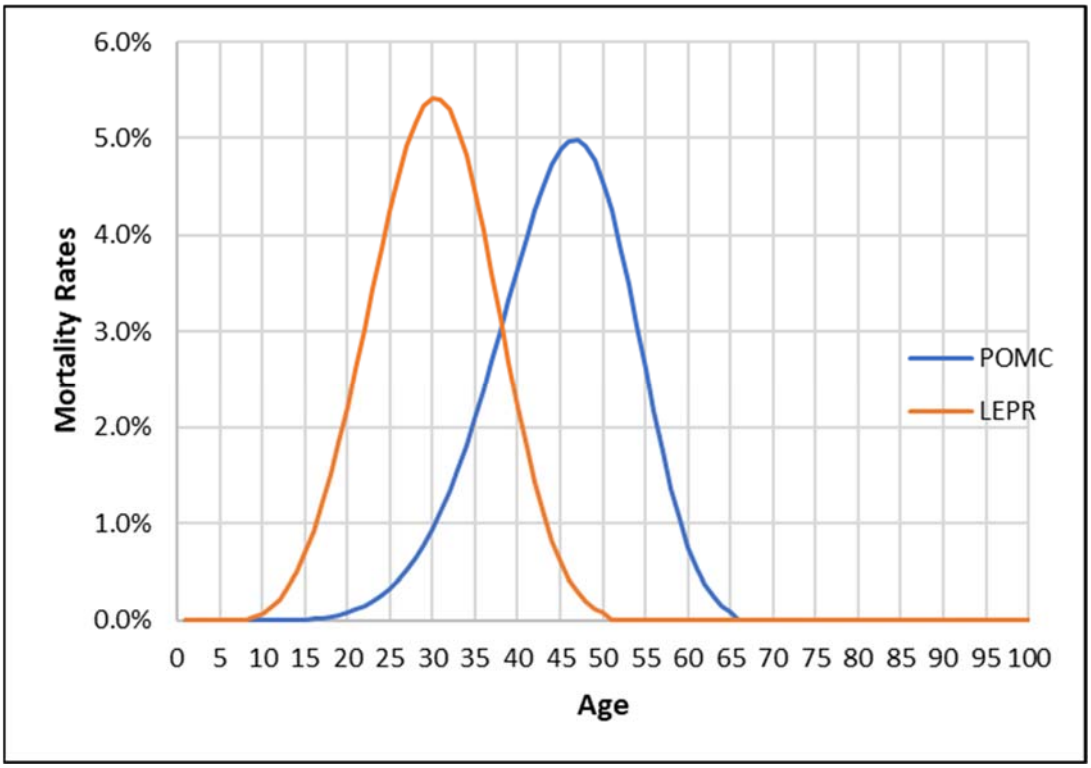
12.2.1.3 *Treatment Effect*

The outcomes from the trials at 52 weeks were used to derive the treatment effect on the natural weight gain trajectories. The natural weight gain trajectories and reduction in weight are summarised in Section 12.2.6. These outcomes were utilised to derive the treatment effect on hyperphagia severity. The baseline distribution of the cohort according to mild, moderate, and severe hyperphagia and the treatment effect on hyperphagia was also explicitly shown in Section 12.2.6. Furthermore, the percentage of individuals who responded to treatment at 12 weeks was used to inform the overall response rate used in the model for the base-case population and different subgroups.

12.2.1.4 ***Mortality***

There is very little evidence in literature on the elevated mortality experienced by patients due to LEPR and POMC/PCSK1 deficiencies. The limited evidence available strongly suggests that these patients experience a very short lifespan as no patients older than 37 years of age were identified in published case reports (2) or enrolled in the setmelanotide clinical trials (2, 86, 87). This challenge is compounded by the fact that the lack of widespread genetic testing for these patients has likely limited the follow-up period in subjects that were identified. Due to this given lack of data on mortality due to LEPR and POMC/PCSK1 deficiencies in the literature , the opinion of a clinical expert (Prof. Farooqi) was used to estimate patient life expectancies (8). The average life expectancy estimates provided were transformed into probability distribution functions. The plots for these functions using a beta distribution are shown in Figure 25 for patients with LEPR (left) and POMC (right) deficiencies, which was also used for the base case. Two alternate distributions (Weibull and Gompertz) were tested in the scenario analyses as a means of testing the sensitivity of the results to the choice of underlying distribution. The distributions chosen are commonly used alternatives to the Weibull distribution.

Figure 25 Probability Distribution Functions for Mortality



Abbreviations: PDF: Probability distribution function; LEPR: Leptin receptor

When untreated or not responding to treatment, LEPR and POMC/PCSK1 deficient patients experience an elevated risk of mortality as a result of early onset of severe obesity and accelerated incidence of comorbidities. Due to general lack of evidence in literature regarding the mortality experienced by these patients, the average life expectancies for these patients are informed based on the opinion of a UK clinical expert and are listed below in Table 68.

However, with a reduction in BMI due to treatment with setmelanotide, these patients can be expected to have a life expectancy more comparable to individuals with general obesity of similar BMI levels according to discussions with a UK clinical expert (Prof Farooqi), although the magnitude of the improvement is dependent upon the specific mutation (8).

The mortality for responders and to treatment with setmelanotide is therefore modelled based on a hazard ratio (HR) derived from data from patients with general obesity applied to all-cause mortality rates for the general population based on life tables for the UK (95). This BMI-stratified HR is informed by a

population-based cohort study comprising 3.6 million adults in the UK (96). as shown in Table 69.

Table 68 Life expectancy of POMC/PCSK1 and LEPR deficient patients

Variable	Value	Reference
Life expectancy, mean age, LEPR	[redacted] years	UK clinical expert opinion (8)
Life expectancy, max age, LEPR	[redacted] years	UK clinical expert opinion (8)
Life expectancy, mean age, POMC/PCSK1	[redacted] years	UK clinical expert opinion (8)
Life expectancy, max age, POMC/PCSK1	[redacted] years	UK clinical expert opinion (8)

Table 69 BMI-based HRs for All-cause Mortality

BMI	HR	Reference
20-25	1.00	UK cohort study (96)
25-30	1.21	UK cohort study (96)
30-35	1.42	UK cohort study (96)
35-40	1.63	UK cohort study (96)
40-45	1.84	UK cohort study (96)
45-50	2.05	UK cohort study (96)
≥50	2.26	UK cohort study (96)

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

An elevated risk of mortality attributable to excess weight in paediatric subjects is also captured as follows. The mapping algorithm prescribed by the World Health Organization (WHO) (90) for mapping the individual BMI to BMI Z-score is used in combination with the BMI-based health states and their respective HRs to derive HRs based on BMI Z-scores.

12.2.1.5 *Utilities*

The economic model was designed to capture the value of setmelanotide considering the impact of treatment on the defective MC4R pathway and, in turn, the effect of treatment on hyperphagia. Thus, the model includes an explicit utility value due to hyperphagia that is assigned as a multiplier to each BMI or BMI-Z health state derived from a vignette study (2).

QoL data was captured in the phase III setmelanotide clinical trials (86, 87) using the short-form, 36-item (SF-36) instrument. However, it is challenging to use these data in the model. Firstly, the reliability of the SF-36 data captured

in the trials is questionable due to the small sample size and lack of data-collection timing standardisation. Secondly, SF-36 is not generalisable to paediatric patients due to the use of a separate patient-reported outcome instrument (the Paediatric Quality of Life Inventory [PedsQL™]). Finally, the SF-36 data recorded in the trial likely implicitly captured some of the effect of hyperphagia on the QoL of these patients but, does not account for it specifically. A vignette study was conducted to identify the specific value of the utility associated with mild, moderate, and severe hyperphagia independent obesity; use of both could lead to double counting of the hyperphagia utility (2). For these reason, EQ-5D utilities from general obesity subjects based on the BMIs and ages reported in literature are used in the model as a conservative assumption.

QoL data was captured in the phase III setmelanotide clinical trials (86, 87) using the short-form, 36-item (SF-36) instrument. However, it is challenging to use these data in the

EQ-5D-based utilities in the paediatric population are informed by the PedsQL™ score reported in Riazi et al. (71) 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 (72). EQ-5D utility values for the remaining BMI Z-score-based health states are then linearly extrapolated using the reported values. The BMI Z-score-based EQ-5D utilities used in the model are shown in Table 70.

Table 70 Mapped EQ-5D Utility for Paediatrics

BMI Z-score	Utility Score	Notes
0.0–1.0	0.89	PedsQL™ reported in Riazi et al. 2010 (71) mapped to EQ-5D scale based on mapping published in Khan et al. 2014 (72)
1.0–2.0	0.87	Extrapolated
2.0–2.5	0.86	Extrapolated
2.5–3.0	0.85	Extrapolated
3.0–3.5	0.83	Extrapolated
3.5–4.0	0.82	PedsQL™ reported in Riazi et al. 2010 (71) mapped to EQ-5D scale based on mapping published in Khan et al. 2014 (72)
≥4.0	0.81	Extrapolated

Abbreviations: BMI: body mass index

The QoL in adults was derived from a published mapping to EQ-5D from SF-12 data (73). A limitation of these data results from the lack of stratification of utility for BMI > 50, which is relevant in the subjects of interest, and LEPR-deficient subjects in particular, and who are often immobile, relatively inactive, and have limited social interactions (8). As no direct evidence exists, scenario analyses with assumptions of decreasing utility for BMI > 50 were explored as described in Table 71.

Table 71 EQ-5D Utilities by BMI and Age

BMI	Age						
	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
25–30	0.91	0.89	0.86	0.83	0.81	0.79	0.79
30–35	0.89	0.86	0.82	0.80	0.79	0.76	0.76
35–40	0.88	0.83	0.79	0.77	0.76	0.74	0.74
40–45	0.84	0.82	0.75	0.73	0.71	0.69	0.69
45–50	0.84	0.82	0.75	0.73	0.71	0.69	0.69
≥50	0.80	0.77	0.70	0.69	0.66	0.66	0.66

Abbreviation: BMI: body mass index

Disutility due to hyperphagia is captured in the model by using a utility multiplier based on the severity of hyperphagia experienced by the individual independent of the BMI or age. This utility multiplier is informed by the vignette study conducted to quantify the impact of hyperphagia alone on QoL (2). This approach was chosen in lieu of what was previously adopted in the metreleptin submission (HST14) which included a QoL decrement based on presence/absence of hyperphagia. The absolute utility decrement, derived based on the chosen DCE methodology, was considered to be an underestimate as it did not fully realize the effect on an individual's quality of life (e.g. members of general public may not fully understand the difference between hyperphagia and usual "hunger"). The vignette study was aimed to better quantify the impact on quality of life based on the severity of hyperphagia experienced. It is implemented in a multiplicative manner for each BMI health state, consistent with established methodology (94). The utility multipliers reported in the study based on the severity of hyperphagia are shown in Table 72.

Table 72 Hyperphagia Utility Multiplier

Hyperphagia Status	Multiplier

Mild	[redacted]	
Moderate	[redacted]	
Severe	[redacted]	

Additionally, the mean disutility attributable to each of the comorbidities are applied on top of this multiplier and considered as absolute utility decrements; these disutilities are implemented in an additive manner in accordance with established methodology (94). Table 73 lists the proportion of each event occurring as a percentage of total CV events and the methodology and source used to derive those proportions. Table 74 lists the annual utility decrements and the references for the values used in the model.

Table 73 Proportion of CV events

Type of CV event	Proportion used in the model	Notes
Myocardial Infarction	35.65%	Calculated as proportion of initial: MI, sudden and non-sudden CHD of total CHD (excl. coronary insufficiency) in D'Agostino, 2000(97) for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino, 2008(98) Assumes an equal ratio of males and females
Angina	39.81%	Calculated as proportion of initial angina of total CHD (excl. coronary insufficiency) in D'Agostino, 2000(97)for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino, 2008(98). Assumes an equal ratio of males and females
Stroke	21.67%	Calculated as the proportion of strokes out of total CHD and strokes in D'Agostino, 2008(98), then multiplied by the proportion of strokes that are not transient ischemic attack from Wolf et al. 1991(99) Assumes an equal ratio of males and females
Transient ischaemic attack (TIA)	6.33%	Calculated as proportion of TIA in total strokes from Wolf et al. 1991(99) in males and females, then multiplied by the proportion of strokes in all CVD events. Assumes an equal ratio of males and females

Abbreviations: Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; TIA = transient ischaemic attack

Table 74 Utility Decrements for Comorbidities

BMI	Disutility	Notes
Sleep apnoea	0.034	Søltoft et al. 2009 The association of body mass index and health-related quality of life in the

		general population: Data from the 2003 Health Survey of England (2009)(74)
Osteoarthritis	0.187	Søltoft et al. 2009 The association of body mass index and health-related quality of life in the general population: Data from the 2003 Health Survey of England (2009)(74)
NAFLD	0.000	No added disutility assumed. Assumption based on the suggestion NAFLD GDG (Guideline Development Group) to consider utility for NAFLD similar to patients with obesity (76)
T2DM	0.043	Søltoft et al. 2009 The association of body mass index and health-related quality of life in the general population: Data from the 2003 Health Survey of England (2009)(74)
CV events	0.064	Sullivan et al. 2011 Catalogue of EQ-5D Scores for the United Kingdom'. Supplementary data. (2011)(75). Weighted based on the percentage of CV events listed in Table 73

Abbreviations: Abbreviations: CV = cardiovascular; NAFLD = non-alcoholic fatty liver disease; T2DM = type 2 diabetes mellitus

12.2.1.6 *Prevalence of Comorbidities*

The prevalence of comorbidities attributable to excess weight due to obesity is informed by evidence found in the literature. This prevalence, stratified by the BMI-based health states, is considered to be same across all age groups due to the lack of data; this is likely a conservative assumption since age is known to have an impact on prevalence of comorbidities.

The prevalence of sleep apnoea attributable to obesity for BMIs 20-25 and 25-30 is based on the prevalence of apnoea-hypopnea index (AHI)≥15 as reported in Young et al for BMI 16-24 and average of prevalence reported for BMI 24-28 and 28-32 respectively (100) The prevalence for BMIs 35–40, 40–50, and ≥50 is derived from a study of morbidly obese patients who underwent weight loss surgery (101). The prevalence for the BMI ≥50 is considered to be an average of the prevalence reported for BMI 50-60 and BMI ≥60 classes in Lopez et al (101).

Table 75 BMI-based Prevalence of Sleep Apnoea

BMI	Prevalence	Notes
20–25	10.00%	Young et al. 2002 (100)
25–30	15.00%	Young et al. 2002 (100); assumed to be average of BMI 24-28 and BMI 28-32
30–35	33.33%	Lopez et al. 2008 (101)
35–40	71.43%	Lopez et al. 2008 (101)

40–45	73.48%	Lopez et al. 2008 (101)
45–50	73.48%	Lopez et al. 2008 (101)
≥50	85.75%	Lopez et al. 2008 (101) Assumed to be an average of BMI 50-60 group and those with BMI≥60

Abbreviation: BMI: body mass index

The prevalence of osteoarthritis, T2DM, and CV events is informed based on results from a cross-sectional survey of adults in England who are eligible for bariatric surgery and included in the model based on the assumptions noted in **Table 76**,**Table 77** and **Table 78** (102). The prevalence of CV events is based on the total prevalence of stroke and coronary heart disease (102).

Table 76 BMI-based Prevalence of Osteoarthritis

BMI	Prevalence	Notes
20–25	6.10%	Ahmad et al.2014 (102) Lower CI of BMI < 35 group
25–30	6.60%	Ahmad et al. 2014 (102) Mean of BMI < 35 group
30–35	10.40%	Ahmad et al. 2014 (102) Average of upper CI of BMI < 35 group and lower CI of BMI 35-40 group
35–40	16.20%	Ahmad et al. 2014 (102) Mean of BMI 35-40 group
40–45	17.00%	Ahmad et al. 2014 (102) Average of upper CI of BMI35-40 group and lower CI of BMI > 40 group
45–50	21.10%	Ahmad et al. 2014 (102) Mean of BMI > 40 group
≥50	26.90%	Ahmad et al. 2014 (102) Upper CI of BMI > 40 group

Abbreviation: BMI: body mass index

Table 77 BMI-based Prevalence of T2DM

BMI	Prevalence	Notes
20–25	2.80%	Ahmad et al. 2014 (102) Lower CI of BMI < 35 group
25–30	3.20%	Ahmad et al. 2014 (102) Mean of BMI < 35 group
30–35	5.20%	Ahmad et al. 2014 (102) Average of upper CI of BMI < 35 group and lower CI of BMI 35-40 group
35–40	8.80%	Ahmad et al. 2014 (102) Mean of BMI 35-40 group
40–45	10.85%	Ahmad et al. 2014 (102) Average of upper CI of BMI35-40 group and lower CI of BMI > 40 group
45–50	16.70%	Ahmad et al. 2014 (102) Mean of BMI > 40 group
≥50	22.50%	Ahmad et al. 2014 (102) Upper CI of BMI > 40 group

Abbreviation: BMI: body mass index; T2DM: Type 2 Diabetes Mellitus

Table 78 BMI-based Prevalence of CV events

BMI	Prevalence	Notes
20–25	3.80%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Lower CI of BMI < 35 group
25–30	4.40%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Mean of BMI < 35 group

30–35	5.25%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Average of upper CI of BMI < 35 group and lower CI of BMI 35-40 group
35–40	8.30%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Mean of BMI 35-40 group
40–45	7.65%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Average of upper CI of BMI35-40 group and lower CI of BMI > 40 group
45–50	10.50%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Mean of BMI > 40 group
≥50	16.80%	Ahmad et al. 2014 (102) Assumed to be the sum of prevalence of stroke and coronary heart disease. Upper CI of BMI > 40 group

Abbreviation: BMI: body mass index; T2DM: CV: cardiovascular

The prevalence of NAFLD in 'normal' weight individuals is reported based on Estes et al (103) while the prevalence of NAFLD for the BMI 40-45 and BMI >=50 groups is based estimates from Mummadi et al. (104) for obese and morbidly obese individuals, respectively. The prevalence for the remaining BMI based health states was linearly interpolated from these values. The inputs used in the model along with the transformations and assumptions are summarized in Table 79.

Table 79 BMI-based Prevalence of NAFLD

BMI	Prevalence	Notes
20–25	21.90%	Estes et al. 2018 Prevalence in UK (all ages) (103)
25–30	43.45%	Linear extrapolation
30–35	65.00%	Extrapolated to 65% and 75% to reach a mean of 70%
35–40	75.00%	Extrapolated to 65% and 75% to reach a mean of 70%
40–45	85.00%	Mummadi et al. 2008 (104)
45–50	90.00%	Linear extrapolation
≥50	95.00%	Mummadi et al. 2008 (104)

Abbreviation: BMI: body mass index; NAFLD: Non-alcoholic fatty liver disease

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Weight loss trajectories reported in the clinical trials (55) were helpful in informing the transitions between the BMI-based health states in the first cycle of the model. Beyond the trial duration, the direction and rate of BMI change in

these patients was defined based on expert clinician opinion (8) as described below.

The rate of BMI change after the trial period was modelled as a constant rate equal to that observed at one year in the pivotal clinical trials (55). Patients with POMC deficiencies are assumed to [redacted] for adults and [redacted] for children. Similarly, the responders with LEPR deficiency are assumed to [redacted] for adults and [redacted] for children. These treatment effect settings are consistent with the patient-level trajectories seen in the long-term extension trials for individuals with LEPR and POMC deficiencies (105).

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The average hunger score recorded in the trials (86, 87) 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 cut-offs for different hyperphagia severities that were considered. A score of 0 - 2.99 (inclusive) translated to mild hyperphagia, 3 - 6.99 translated to moderate hyperphagia, and 7 - 10 translated to severe hyperphagia. These hunger score cut-offs and scale mappings were derived from discussion with clinical experts. The mappings of hunger score to hyperphagia were used to relate the utility scores for mild, moderate, and severe hyperphagia derived from a vignette study (2) in the economic model.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No serious treatment-related adverse events were reported in the clinical trials (55). The most commonly reported adverse events included injection site reactions, skin disorders (e.g., hyperpigmentation), and nausea in the POMC/PCSK1 (87) and LEPR (86) trials, although none led to withdrawal or death. Additionally, none of the serious adverse events were considered to be related to the treatment. As a result, adverse events were not included in the model.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Expert opinion of several clinical advisers on key model parameters, inputs and assumptions was sought during the development of the cost-effectiveness analysis for setmelanotide. These experts include Professor Sadaf Farooqi, Professor Julian Hamilton-Shield and Professor John Wilding. They were selected on the grounds of either being KOLs in the fields of MC4R deficiency or obesity and metabolic diseases for adults and paediatrics in the UK. Rhythm Pharmaceuticals interviewed all participants and asked the same questions about the impact of the disease on patients and how it differs from general obesity. No background information was provided to the clinical experts prior to the discussions. Opinions were collated descriptively, and interviews were carried out via Teams using a pre-defined questionnaire. There was no financial reimbursement for the consultation with any of the clinical experts.

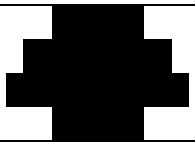
12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Table 80 below.

All variables included in the cost-effectiveness analysis for setmelanotide are shown in Table 80.

Table 80 Summary of Variables

Parameters	Base-case Values	Sources
Health state utilities	See Table 67 and Table 69	
Health state costs	See Table 83	
Patient characteristics		
% POMC	33.30%	Graves et al. 2021(106) Kleinendorst et al. 2020(107) Stijnen et al. 2016(108)
% LEPR	66.70%	
% Paediatric	74.00%	Argente et al. 2019(109)
% Adult	26.00%	
Mean age, POMC adult	25.4	Based on clinical trials (NCT02896192 and NCT03287960)(86, 87)
Mean age, LEPR adult	26.3	
% female, POMC adult	40.0%	
% female, LEPR adult	60.0%	

Mean age, POMC paediatric	12.8	
Mean age, LEPR paediatric	12.4	
% female, POMC paediatric	33.33%	
% female, LEPR paediatric	60.00%	
Baseline BMI distribution, POMC (20–25, 25–30, 30–35, 35–40, 40–45, 45–50, and ≥50)	[redacted]	Based on a clinical trial (NCT02896192) (87)
Baseline BMI distribution, LEPR (20–25, 25–30, 30–35, 35–40, 40–45, 45–50, and ≥50)	[redacted]	Based on a clinical trial (NCT03287960) (86)
BMI Z-score distribution, POMC (0.0–1.0, 1.0–2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and ≥4.0)	[redacted]	Based on a clinical trial (NCT02896192) (87)
BMI Z-score distribution, LEPR (0.0–1.0, 1.0–2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and ≥4.0)	[redacted]	Based on a clinical trial (NCT03287960) (86)
Mild Hyperphagia, POMC	[redacted]	Assumption based on UK clinical expert (8)
Mild Hyperphagia, LEPR	[redacted]	Assumption based on UK clinical expert (8)
Moderate Hyperphagia, POMC	[redacted]	Assumption based on UK clinical expert (8)
Moderate Hyperphagia, LEPR	[redacted]	Assumption based on UK clinical expert (8)
Severe Hyperphagia, POMC	[redacted]	Assumption based on UK clinical expert (8)
Severe Hyperphagia, LEPR	[redacted]	Assumption based on UK clinical expert (8)
Natural weight gain		

Natural weight gain, POMC adult	0 levels	Assumed weight stabilised after adulthood
Natural weight gain, POMC paediatric	0 levels	Assumed natural weight gain does not impact BMI Z-score level
Natural weight gain, LEPR adult	0 levels	Assumed weight stabilised after adulthood
Natural weight gain, LEPR paediatric	0 levels	Assumed natural weight gain does not impact BMI Z-score level
Treatment effect		
Response rate, POMC adult	86%	Based on a clinical trial (NCT02896192) (87)
Response rate, LEPR adult*	60%	Based on a clinical trial (NCT03287960) (86)
Response rate, POMC paediatric	86%	Based on a clinical trial (NCT02896192) (87)
Response rate, LEPR paediatric*	60%	Based on a clinical trial (NCT03287960) (86)
Expected treatment efficacy after trial duration, POMC		Assumption based on UK clinical expert (8)
Expected treatment efficacy after trial duration, LEPR		Assumption based on UK clinical expert (8)
BMI drop during trial, POMC adult		Based on a clinical trial (NCT02896192) (87)
BMI drop during trial, LEPR adult		Based on a clinical trial (NCT03287960) (86)
BMI drop during trial, POMC paediatric		Based on a clinical trial (NCT02896192) (87)
BMI drop during trial, LEPR paediatric		Based on a clinical trial (NCT03287960) (86)
BMI drop after trial, POMC adult		Assumption
Lowest BMI class, POMC adult		Assumption based on UK clinical expert (8)
Lowest BMI Z-score class, POMC paediatric		Assumption based on UK clinical expert (8) and mapping of BMI-Z score classes to BMI-based classes
BMI change after trial, LEPR		Assumption based on UK clinical expert (8)
Transition: Severe to mild Hyperphagia, POMC		Based on internal analysis conducted by Rhythm Pharmaceuticals
Transition: Severe to moderate Hyperphagia, POMC		Based on internal analysis conducted by Rhythm Pharmaceuticals

Transition: Moderate to Mild Hyperphagia, POMC	[redacted]	Based on internal analysis conducted by Rhythm Pharmaceuticals
Transition: Severe to mild Hyperphagia, LEPR	[redacted]	Based on internal analysis conducted by Rhythm Pharmaceuticals
Transition: Severe to moderate Hyperphagia, LEPR	[redacted]	Based on internal analysis conducted by Rhythm Pharmaceuticals
Transition: Moderate to Mild Hyperphagia, LEPR	[redacted]	Based on internal analysis conducted by Rhythm Pharmaceuticals

Abbreviations: BMI = body mass index; LEPR = leptin receptor; NCT = national clinical trial; POMC = pro-opiomelanocortin

*The response rate to the primary end point in the trial was 53%, however it was felt that the primary endpoint could miss some patients who were considered to have a clinical response to setmelanotide, particularly paediatric patients who are increasing in height during the 52 weeks of the trial and for whom a <10% decrease in body weight from baseline is likely to be deemed clinically significant. Increasing the response rate from 53% to 60% is representative of one patient out of the 15 in the trial responding clinically while missing the primary endpoint.

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The common medical resource utilisation (MRU) components utilised by these patients include an annual complete blood count, liver function test, comprehensive metabolic panel, and regular physician visits to monitor their health status and identify any risks attributable to excess weight (2). Expert clinician opinions were used to inform the frequency of monitoring visits required for setmelanotide and the comparators; it is presented in Table 81 and Table 82, along with their unit costs (2).

Table 81 MRU Annual Frequencies

Resources	Setmelanotide + BSC	BSC
Complete blood count	1	1
Liver function test	1	1
Comprehensive metabolic panel	1	1
Physician visit	1	4

Abbreviation: BSC = best supportive care; MRU: Medical resource utilisation

Table 82 Unit Costs of MRU

Resources	Unit Costs	References

Complete blood count	£2.79	National Schedule of NHS costs - Year 2018-19(110) Unit Costs of Health and Social Care 2020(111)
Liver function test	£8.79	
Comprehensive metabolic panel	£15.38	
Physician visit	£39.23	Physician visit based on general practitioner visit (per patient contact lasting 9.22 min)

Abbreviations: ISBN = International Standard Book Number; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

Resource identification, measurement, and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria and consider published and unpublished studies.

Searches for relevant evidence yielded 594 records from electronic literature databases. After the removal of duplicates, there were 579 unique abstracts eligible for title and abstract screening. Of these, 36 publications were identified for full-text screening. None of the studies identified through database searches were deemed to meet the criteria for inclusion in the economic burden SLR. Furthermore, no additional relevant studies were identified through grey literature sources hence, no studies met the inclusion criteria for the economic burden of disease SLR (see Appendix 3).

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Inputs to the resource used in the economic model was sought from the same clinical experts and the same methodology of interactions was applied as described in Section Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Two major steps were taken to ensure the applicability of the resources and costs used in the model for patients with obesity associated with LEPR or POMC/PCSK1 deficiency treated in England. Interviews of three clinical experts in the treatment of obesity in the UK, including Prof. James Wilding an expert in general obesity, Prof. Sadaf Farooqi, a world-recognized expert in

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

the treatment of patients with the specific conditions noted above, and Prof. Hamilton-Shield, a specialist in the treatment of paediatric subjects, including patients with rare genetic diseases of obesity, were conducted to support the submission and development of the economic model. These interviews served to provide expert guidance on the use of surrogate data to fill material evidence gaps, better understand the differences between the LEPR and POMC/PCSK1-deficient subpopulations from a clinical perspective and provide guidance on the expected clinical use of setmelanotide and benefits in these patients to inform key model assumptions. There was no financial reimbursement for the consultation with any of the clinical experts.

Furthermore, the development of the de novo model has, where relevant made use of existing data and relevant features of cost-effectiveness analyses developed for past NICE appraisals.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The reference NHS list price for setmelanotide is [redacted]/mg. Administration costs are not considered in the model, as the training for self-injection is expected to be provided so that the individuals will be able to self-administer the treatment dose daily.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

The list price is used in the economic model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model.

The costs associated with setmelanotide and the comparator are restricted to treatment and routine monitoring costs; these costs are shown in Table 83 and Table 84.

Table 83 Cost per Treatment/Patient Associated with Setmelanotide

Items	Values	Notes
Price of the technology per mg	[redacted]	NHS list price of setmelanotide without PAS
Administration costs	£0.00 (self-administration)	

Monitoring costs	£66.19	Frequency: Based on KOL inputs Unit costs: National Schedule of NHS costs - Year 2018-19(110) Unit Costs of Health and Social Care 2020(111)
Total annual costs per treatment/patient	[redacted] (year 1) [redacted] (years 2+)	Annual costs in year 1 based on an average dose of [redacted] mg/day and years 2+ based on [redacted]mg/day

Abbreviations: ISBN = International Standard Book Number; KOL = key opinion leader; NHS = National Health Service; PAS = Patient access scheme; PSSRU = Personal Social Services Research Unit

Table 84 Costs per Treatment/Patient Associated with the Comparator

Items	Values	Notes
Price of the comparator per unit	£0	Covered under the obesity management costs
Administration costs	£0.00	Not applicable
Monitoring costs	£183.88	Frequency: Based on KOL inputs. Unit costs: National Schedule of NHS costs - Year 2018-19(110) Unit Costs of Health and Social Care 2020(111)
Total annual costs per treatment/patient	£0.00	Diet and exercise changes are assumed to incur negligible costs aside from physician consultation visits that are accounted for elsewhere

Abbreviations: ISBN = International Standard Book Number; KOL = key opinion leader; NHS = National Health Service; PSSRU = Personal Social Services Research Unit

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Obesity management costs used in the model are informed by Curtis and Burns et al, Ara et al., and NHS reference costs from 2012, 2017, and 2018 (101, 119, and 154), which are inflated to the 2021 £ value. Annual management costs for comorbidities are also inflated to the 2021 £ value and presented in Table 85.

Annual costs for management of CV events are based on a weighted average of long-term costs of each event weighted by the proportion of the event occurring in total CV events. The acute cost of CV events is not accounted for in the overall cost of CV events as new incidence of such events cannot be tracked under the existing model structure which is implemented on

prevalence rates; a scenario analysis was run to explore the effect of some fraction of the annual prevalence of CV events arising from newly incident acute events. The inputs used in the model for the composite CV endpoints are listed in Table 73.

Table 85 Disease Management Costs

Type of CV Event	Proportion used in the model	Notes
Obesity management costs (all health states)	£140.82	Table 35 Curtis and Burns, 2017 (112), Ara et al., 2012(113) NHS Reference Costs 2017/2018 (101, 119, 154)(114)
Annual cost of sleep apnoea	£1,681	Table 35 McMillan et al. 2015 (115)
Annual cost of osteoarthritis	£1,066.70	Table 31 Oxford Economics. The economic costs of arthritis for the UK economy. Final Report. March 2010(116)
Annual cost of NAFLD	£394.41	Table 5. Younossi et al. 2016(117)
Annual cost of T2DM	£3,459.99	Table 1 Currie et al. 2007 (118)
Annual cost of CV events	£2,823.52	Weighted average for individual CV events costs based on the proportions of each event listed in Table 73
Annual cost of MI	£2,472.28	Table 2. Danese et al. 2016(119)
Annual cost of Angina	£2,179.64	Table 2. Danese et al. 2016(119)
Annual cost of Stroke	£2,545.10	Table 2. Danese et al. 2016(119)
Annual cost of TIA	£2,447.92	Table 2. Danese et al. 2016(119)

Abbreviations: CV = cardiovascular; ID = identification number; NAFLD = non-alcoholic fatty liver disease; NHS = National Health Service; T2DM = type 2 diabetes mellitus; UK = United Kingdom

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Adverse events and the associated costs were not included in the model.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

The model base case does not include costs to caregivers and drug administration costs, such as home delivery and self-administration.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Social stigma, peer pressure, psychological issues, and an inability to perform at school or work are issues not included in the model. This provides additional opportunities for resource savings as the issues noted represent substantial levels of unquantifiable health and non-health benefits in the QoL of caregivers/families of children and adults with obesity due to LEPR or POMC/PCSK1 deficiencies. It is anticipated that the treatment of children with POMC/PCSK1 or LEPR deficiencies with setmelanotide may attenuate these mental health issues over time as BMI reductions are achieved and provide further opportunities for unquantified health benefits and resource savings.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-effectiveness analysis.

The following sensitivity analyses were conducted in the model:

- Deterministic one-way sensitivity analyses (OWSA) was conducted on all applicable parameters using either 10% or 20% where applicable.

- Scenario analyses were conducted to assess the impact of varying multiple inputs and to explore the uncertainty around the structural assumptions used in the model. The different scenarios are outlined in

- Probabilistic sensitivity analysis (PSA): Distributions were selected in Table 87 line with recommendations made by Briggs et al., incorporating uncertainty around parameter estimates into cost-effectiveness modelling. The PSA was conducted encompassing a total of 1000 cohort runs to ensure stable results. A cost-effectiveness acceptability curve was generated across 201 willingness to pay thresholds (£0- £500,000 in equal increments of £2,500).

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analyses and PSAs were undertaken, as described above. All costs included in the model, except for treatment costs, were varied by ±20%. Parameters related to baseline patient characteristics, treatment effect, utility values, and mortality were varied by ±10%. All other variables included in the OWSA along with their range of values are described in Table 21 below. Parameters varied in the PSA along with their respective

12.4.3 Complete table Table 86, Table **87** and Table **88** as appropriate to summarise the variables used in the sensitivity analysis.

Table 86 Variables used in one-way scenario-based deterministic sensitivity analysis

Variables	Base-case value	Lower bound value	Upper bound value
Time horizon	Lifetime	10 years	20 years
Discount rate - costs	3.5%	0.0%	1.5%
Discount rate - health	1.5%	0.0%	3.5%
% Cohort – POMC (±10%)	33.3%	30.0%	36.6%
% Cohort – Pediatric (±10%)	74.0%	66.6%	81.4%
% Female (±10%)	60.0%	54.0%	66.0%
Pediatric mean age	POMC: 12.8, LEPR: 12.4	11 years	15 years
Adult mean age	POMC: 25.4, LEPR: 26.3	24 years	28 years

Pediatric natural weight gain	POMC: 0 level(s) every 5 year(s), LEPR: 0 level(s) every 5 year(s)	1 level every 2 years	1 level every 4 years
Adult natural weight gain	POMC: 0 level(s) every 5 year(s) LEPR: 0 level(s) every 5 year(s)	1 level every 3 years	1 level every 5 years
Response rate (±10%)	60%	54%	66%
Treatment efficacy (±1 level(s))	[redacted] levels of BMI/BMI Z-score drop from baseline	1 level of BMI/BMI Z-score drop from baseline	3 levels of BMI/BMI Z-score drop from baseline
Treatment effect after trial duration - POMC (BMI regain, BMI maintenance)	[redacted]	Regain 1 BMI/BMI Z-score level every 4 years after 3 years	Maintain BMI level observed at the end of trial
Treatment effect after trial duration - LEPR (BMI regain, Continue BMI loss)	[redacted]	Regain 1 BMI/BMI Z-score level every 4 years after 3 years	Continue BMI loss until BMI 35-40 / BMI Z-score 2.5-3.0
Treatment effect on hyperphagia - Severe to mild (±10%)	POMC: [redacted] LEPR: [redacted]	POMC: 60.0% LEPR: 45.0%	POMC: 73.4% LEPR: 55.0%
Treatment effect on hyperphagia - Severe to moderate (±10%)	POMC: [redacted] LEPR: [redacted]	POMC: 29.9% LEPR: 45.0%	POMC: 36.7% LEPR: 55.0%
Treatment effect on hyperphagia - Moderate to mild (±10%)	POMC: [redacted] LEPR: [redacted]	POMC: 36.0% LEPR: 67.5%	POMC: 44.0% LEPR: 82.5%
Setmelanotide dose after trial duration (1.5 mg, 2.2 mg)	1.8 mg	1.5 mg	2.2 mg
BSC cost (±20%)	£140.82	£112.65	£168.98
Monitoring cost (±20%)	Setmelanotide+BSC= £66.19 BSC= £183.88	Setmelanotide+BSC= £52.95 BSC= £147.11	Setmelanotide+BSC= £79.43 BSC= £ £220.66
Comorbidity management costs	Sleep apnea= £1,681.11 Osteoarthritis= £1,066.70 NAFLD= £394.41 T2DM= £3,459.99	Sleep apnea= £1,344.89 Osteoarthritis= £853.36 NAFLD= £315.53 T2DM= £2,768.00	Sleep apnea= £2,017.33 Osteoarthritis= £1,280.03 NAFLD= £473.30 T2DM= £4,151.99

	CV events= £2,823.52	CV events= £2,258.82	CV events= £3,388.22
Hyperphagia utility multiplier (±10%)	Mild= 0.909 Moderate=0.702 Severe=0.218	Mild= 0.818 Moderate=0.632 Severe=0.196	Mild= 1.000 Moderate=0.772 Severe=0.240
Disutility associated with comorbidities (±10%)	Sleep apnea= 0.034 Osteoarthritis= 0.187 NAFLD= 0.000 T2DM= 0.043 CV events= 0.066	Sleep apnea= 0.030 Osteoarthritis= 0.168 NAFLD= 0.000 T2DM= 0.038 CV events= 0.059	Sleep apnea= 0.037 Osteoarthritis= 0.205 NAFLD= 0.000 T2DM= 0.047 CV events= 0.072
Life expectancy for untreated patients - distribution	Weibull	Log-logistic	Beta
Life expectancy for untreated patients - mean age (±10 years)	LEPR: 30 years POMC: 45 years	LEPR: 20 years POMC: 35 years	LEPR: 40 years POMC: 55 years
Life expectancy for untreated patients - max age (±10 years)	LEPR: 50 years POMC: 65 years	LEPR: 40 years POMC: 55 years	LEPR: 60 years POMC: 75 years
All-cause mortality HRs - adult (±10%)	BMI 20-25= 1.00 BMI 25-30= 1.21 BMI 30-35= 1.42 BMI 35-40= 1.63 BMI 40-45= 1.84 BMI 45-50= 2.05 BMI ≥50= 2.26	BMI 20-25= 0.90 BMI 25-30= 1.09 BMI 30-35= 1.28 BMI 35-40= 1.47 BMI 40-45= 1.66 BMI 45-50= 1.85 BMI ≥50= 2.03	BMI 20-25= 1.10 BMI 25-30= 1.33 BMI 30-35= 1.56 BMI 35-40= 1.79 BMI 40-45= 2.02 BMI 45-50= 2.26 BMI ≥50= 2.49

Abbreviations: BMI = body mass index; BSC = best supportive care; CV = cardiovascular; HR = hazard ratio; LEPR = leptin receptor; NAFLD = non-alcoholic fatty liver disease; POMC = pro-opiomelanocortin T2DM = type 2 diabetes mellitus

Table 87 Variables used in multi-way scenario-based sensitivity

Scenario	Description	Justification
1	Patients uniformly distributed amongst the BMI/BMI Z-score based health states starting at BMI Z-score 2.0-2.5 for paediatric and BMI 30-35 for adult patients at baseline	To provide insight to the change in outcomes when the baseline distribution of patients is not based on the observed data in the clinical trials (86, 87)
2	Percent distribution of POMC and LEPR patients based on population observed in the clinical trials (86, 87)	To provide insight to the change in outcomes by using data directly from the clinical trials (86, 87)
3	Percent distribution of paediatric and adult patients	To provide insight to the change in outcomes by using data directly from the clinical trials (86, 87)

	based on population observed in the clinical trials (86, 87)	
4	All patients responding to treatment with setmelanotide have 1 level improvement in their hyperphagia severity	As the impact of hyperphagia may not be fully realized solely by reduction in hunger scores, this provides an insight to the change in outcomes by using alternative data based on UK clinical expert opinion
5	Inclusion of comorbidities that are prevalent in paediatric population only i.e. sleep apnoea, osteoarthritis, and NAFLD	To provide insight to the change in outcomes by only including the comorbidities having the most prevalence in these patients
6	Increase in BSC costs by £25 per BMI/BMI Z-score level increase	To provide insight to the change in outcomes and explore if there is any cost savings associated with increasing BSC costs with increasing BMI/BMI Z-score
7	Response rates stratified by age groups observed in the clinical trials (86, 87)	To provide insight to the change in outcomes by using data directly from the clinical trials (86, 87)
8	Hyperphagia severity at baseline and effect of treatment determined based on the worst hunger score collected in the clinical trials (86, 87)	To provide insights to the change in outcomes if the worst hunger score collected in the clinical trials(86, 87) is used to derive hyperphagia severity at baseline and the effect of treatment on it
9	Increased disutility due to presence of obesity-related comorbidities	To provide insights to the change in outcomes as these patients are believed to experience more severe forms of these comorbidities
10	Accounting for acute cost of CV events	To provide insights to the change in outcomes by considering acute CV event costs by assuming 25% of prevalent cases accrue acute event costs in each cycle
11	Utility scores decreased by 0.05 for BMI ≥ 50	To provide insights to the change in outcomes by exploring the impact of decreasing utility for patients with severe obesity by 0.05

Abbreviations: BMI = body mass index; BSC = best supportive care; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; LEPR = leptin receptor; NAFLD = non-alcoholic fatty liver disease; NHS = National Health Service; POMC = pro-opiomelanocortin

Table 88 Variables used in probabilistic sensitivity analysis

Variable	Mean base-case value	Distribution
% Cohort, POMC	33.3%	Normal
% Cohort, Paediatric	74.0%	Normal
Overall response rate, Paediatric	60%	Normal
Overall response rate, Adult	60%	Normal

Effect on hyperphagia by severity, severe to mild	50%	Dirichlet
Effect on hyperphagia by severity, severe to moderate	50%	Dirichlet
Effect on hyperphagia by severity, moderate to mild	0%	Dirichlet
Effect on hyperphagia by severity, moderate to mild	75%	Normal
BSC Cost, BMI Z-score 0.0-1.0	£141	Gamma
BSC Cost, BMI Z-score 1.0-2.0	£141	Gamma
BSC Cost, BMI Z-score 2.0-2.5	£141	Gamma
BSC Cost, BMI Z-score 2.5-3.0	£141	Gamma
BSC Cost, BMI Z-score 3.0-3.5	£141	Gamma
BSC Cost, BMI Z-score 3.5-4.0	£141	Gamma
BSC Cost, BMI Z-score ≥4.0	£141	Gamma
BSC Cost, BMI 20-25	£141	Gamma
BSC Cost, BMI 25-30	£141	Gamma
BSC Cost, BMI 30-35	£141	Gamma
BSC Cost, BMI 35-40	£141	Gamma
BSC Cost, BMI 40-45	£141	Gamma
BSC Cost, BMI 45-50	£141	Gamma
BSC Cost, BMI 50-55	£141	Gamma
BSC Cost, BMI 55-60	£141	Gamma
BSC Cost, BMI 60-65	£141	Gamma
BSC Cost, BMI 65-70	£141	Gamma
BSC Cost, BMI ≥70	£141	Gamma
Monitoring Cost, setmelanotide + BSC	£66	Gamma
Monitoring Cost, BSC	£184	Gamma
Sleep apnoea management cost	£1,681	Gamma
Osteoarthritis management cost	£1,067	Gamma
NAFLD management cost	£394	Gamma
T2DM management cost	£3,460	Gamma
CV events management cost	£2,824	Gamma
Utility, age 6-18, BMI Z-score 0.0-1.0	0.89	Beta
Utility, age 6-18, BMI Z-score 1.0-2.0	0.87	Beta
Utility, age 6-18, BMI Z-score 2.0-2.5	0.86	Beta
Utility, age 6-18, BMI Z-score 2.5-3.0	0.85	Beta
Utility, age 6-18, BMI Z-score 3.0-3.5	0.83	Beta
Utility, age 6-18, BMI Z-score 3.5-4.0	0.82	Beta
Utility, age 6-18, BMI Z-score ≥4.0	0.81	Beta
Utility, age 19-29, BMI 20-25	0.91	Beta
Utility, age 19-29, BMI 25-30	0.91	Beta
Utility, age 19-29, BMI 30-35	0.89	Beta
Utility, age 19-29, BMI 35-40	0.88	Beta

Utility, age 19-29, BMI 40-45	0.84	Beta
Utility, age 19-29, BMI 45-50	0.84	Beta
Utility, age 19-29, BMI 50-55	0.80	Beta
Utility, age 19-29, BMI 55-60	0.80	Beta
Utility, age 19-29, BMI 60-65	0.80	Beta
Utility, age 19-29, BMI 65-70	0.80	Beta
Utility, age 19-29, BMI ≥70	0.80	Beta
Utility, age 30-39, BMI 20-25	0.89	Beta
Utility, age 30-39, BMI 25-30	0.89	Beta
Utility, age 30-39, BMI 30-35	0.86	Beta
Utility, age 30-39, BMI 35-40	0.83	Beta
Utility, age 30-39, BMI 40-45	0.82	Beta
Utility, age 30-39, BMI 45-50	0.82	Beta
Utility, age 30-39, BMI 50-55	0.77	Beta
Utility, age 30-39, BMI 55-60	0.77	Beta
Utility, age 30-39, BMI 60-65	0.77	Beta
Utility, age 30-39, BMI 65-70	0.77	Beta
Utility, age 30-39, BMI ≥70	0.77	Beta
Utility, age 40-49, BMI 20-25	0.86	Beta
Utility, age 40-49, BMI 25-30	0.86	Beta
Utility, age 40-49, BMI 30-35	0.82	Beta
Utility, age 40-49, BMI 35-40	0.79	Beta
Utility, age 40-49, BMI 40-45	0.75	Beta
Utility, age 40-49, BMI 45-50	0.75	Beta
Utility, age 40-49, BMI 50-55	0.70	Beta
Utility, age 40-49, BMI 55-60	0.70	Beta
Utility, age 40-49, BMI 60-65	0.70	Beta
Utility, age 40-49, BMI 65-70	0.70	Beta
Utility, age 40-49, BMI ≥70	0.70	Beta
Utility, age 50-59, BMI 20-25	0.83	Beta
Utility, age 50-59, BMI 25-30	0.83	Beta
Utility, age 50-59, BMI 30-35	0.80	Beta
Utility, age 50-59, BMI 35-40	0.77	Beta
Utility, age 50-59, BMI 40-45	0.73	Beta
Utility, age 50-59, BMI 45-50	0.73	Beta
Utility, age 50-59, BMI 50-55	0.69	Beta
Utility, age 50-59, BMI 55-60	0.69	Beta
Utility, age 50-59, BMI 60-65	0.69	Beta
Utility, age 50-59, BMI 65-70	0.69	Beta
Utility, age 50-59, BMI ≥70	0.69	Beta
Utility, age 60-69, BMI 20-25	0.81	Beta
Utility, age 60-69, BMI 25-30	0.81	Beta
Utility, age 60-69, BMI 30-35	0.79	Beta

Utility, age 60-69, BMI 35-40	0.76	Beta
Utility, age 60-69, BMI 40-45	0.71	Beta
Utility, age 60-69, BMI 45-50	0.71	Beta
Utility, age 60-69, BMI 50-55	0.66	Beta
Utility, age 60-69, BMI 55-60	0.66	Beta
Utility, age 60-69, BMI 60-65	0.66	Beta
Utility, age 60-69, BMI 65-70	0.66	Beta
Utility, age 60-69, BMI ≥70	0.66	Beta
Utility, age 70-79, BMI 20-25	0.79	Beta
Utility, age 70-79, BMI 25-30	0.79	Beta
Utility, age 70-79, BMI 30-35	0.76	Beta
Utility, age 70-79, BMI 35-40	0.74	Beta
Utility, age 70-79, BMI 40-45	0.69	Beta
Utility, age 70-79, BMI 45-50	0.69	Beta
Utility, age 70-79, BMI 50-55	0.66	Beta
Utility, age 70-79, BMI 55-60	0.66	Beta
Utility, age 70-79, BMI 60-65	0.66	Beta
Utility, age 70-79, BMI 65-70	0.66	Beta
Utility, age 70-79, BMI ≥70	0.66	Beta
Utility, age 80+, BMI 20-25	0.79	Beta
Utility, age 80+, BMI 25-30	0.79	Beta
Utility, age 80+, BMI 30-35	0.76	Beta
Utility, age 80+, BMI 35-40	0.74	Beta
Utility, age 80+, BMI 40-45	0.69	Beta
Utility, age 80+, BMI 45-50	0.69	Beta
Utility, age 80+, BMI 50-55	0.66	Beta
Utility, age 80+, BMI 55-60	0.66	Beta
Utility, age 80+, BMI 60-65	0.66	Beta
Utility, age 80+, BMI 65-70	0.66	Beta
Utility, age 80+, BMI ≥70	0.66	Beta
Mild hyperphagia utility multiplier	0.91	Beta
Moderate hyperphagia utility multiplier	0.70	Beta
Severe hyperphagia utility multiplier	0.22	Beta
Disutility associated with sleep apnoea	0.03	Beta
Disutility associated with osteoarthritis	0.19	Beta
Disutility associated with NAFLD	0.00	Beta
Disutility associated with T2DM	0.04	Beta
Disutility associated with CV events	0.07	Beta
Mean adult life expectancy, POMC	[redacted] year(s)	Normal
Max Adult life expectancy, POMC	[redacted] year(s)	Normal
Mean adult life expectancy, LEPR	[redacted] year(s)	Normal
Max Adult life expectancy, LEPR	[redacted] year(s)	Normal
All-cause mortality HR, BMI 20-25	1.00	Normal

All-cause mortality HR, BMI 25-30	1.21	Normal
All-cause mortality HR, BMI 30-35	1.42	Normal
All-cause mortality HR, BMI 35-40	1.63	Normal
All-cause mortality HR, BMI 40-45	1.84	Normal
All-cause mortality HR, BMI 45-50	2.05	Normal
All-cause mortality HR, BMI 50-55	2.26	Normal
All-cause mortality HR, BMI 55-60	2.47	Normal
All-cause mortality HR, BMI 60-65	2.68	Normal
All-cause mortality HR, BMI 65-70	2.89	Normal
All-cause mortality HR, BMI ≥70	3.10	Normal

Abbreviations: BMI = body mass index; BSC = best supportive care; HR = hazard ratio; LEPR = leptin receptor; NAFLD = non-alcoholic fatty liver disease; POMC = pro-opiomelanocortin

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

The cost of setmelanotide remained fixed in the model base case.

Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

12.5 Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

The base-case cost-effectiveness results are presented in Table 89 below. Setmelanotide + BSC accrued [redacted] incremental QALYs and £2,620,816 incremental costs over a lifetime time horizon. This corresponds to an ICER of £176,913 per additional QALY gained over BSC alone. Table 89 below presents results for both a cohort including patients with both LEPR and POMC/PCSK1 deficiencies as well as separate results for LEPR and POMC/PCSK1 deficient cohorts.

Table 89 Base-case results - discounted

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Incremental (QALYs)
Setmelanotide + BSC, LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,147
BSC LEPR	£25,233	12.01	2.73	-	-	-	-
Setmelanotide + BSC, POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£189,215
BSC POMC	£40,903	21.77	6.35	-	-	-	-
Setmelanotide + BSC overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,913 (weighted average)
BSC overall	£30,451	15.26	3.94	-	-	-	-

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The clinical trials (86, 87) for LEPR and POMC/PCSK1 deficient patients were both single-arm phase 3 trials. As a result, outcomes from the model were not compared with the clinical trial results as no head-to-head trials compared setmelanotide with BSC in patients POMC/PCSK1 or LEPR deficient patients.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The model uses a Markov structure and the health states in the model represent the current BMI/BMI Z-score levels of these patients and death. Therefore, this is not appropriate.

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are accrued in patients on a per-cycle basis over the course of model lifetime. The Markov states a patient resides in, determines the utilities for the patients. These utilities are based on the current age and BMI/BMI Z-score level of the patients. A utility decrement is then generated based on the proportion of cohort residing in that health state and experiencing the obesity-related comorbidities included in the model. In addition to this decrement, another decrement is generated based on the severity of hyperphagia experienced by these patients which is subtracted from the age and BMI/BMI Z-score dependent utilities. QALYs are then summed across all cycles in the model, with each cycle's resultant QALY value discounted appropriately.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The model uses a Markov structure and the health states represented in the model represent the current BMI/BMI Z-score levels of these patients and death. Therefore, this is not appropriate.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The model uses a Markov structure and the health states represented in the model represent the current BMI/BMI Z-score levels of these patients and death. Therefore, this is not appropriate.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

The undiscounted base-case cost-effectiveness results using the PAS are presented in Table 90 below. Setmelanotide + BSC accrued [redacted] undiscounted incremental QALYs and [redacted] incremental costs over a lifetime time horizon. This corresponds to an ICER of £281,796 per additional QALY gained over BSC alone. Table 90 below presents results for both a cohort including patients with both LEPR and POMC/PCSK1 deficiencies as well as separate results for LEPR and POMC/PCSK1 deficient cohorts.

Table 90 Base-case results - undiscounted

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Incremental (QALYs)
Setmelanotide + BSC, LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£273,224
BSC LEPR	£35,259	13.91	3.02	-	-	-	-
Setmelanotide + BSC, POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£294,822
BSC POMC	£68,371	27.45	7.56	-	-	-	-
Setmelanotide + BSC overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£281,796 (weighted average)
BSC overall	£46,285	18.42	4.53	-	-	-	-

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table 91.

Table 91 Summary of costs by category of cost per patient

Items	Cost (Setmelanotide+BSC)	Cost (BSC)	Increment	Absolute Increment	% Absolute Increment
Mean total treatment costs	[redacted]	£1,769	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£2,310	[redacted]	[redacted]	[redacted]
Comorbidity -related costs	[redacted]	£26,371	[redacted]	[redacted]	[redacted]
Total	[redacted]	**£30,451**	[redacted]	[redacted]	[redacted]

Adapted from the Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state.

The model uses a Markov structure and the health states represented in the model represent the current BMI/BMI Z-score levels of these patients and death. Therefore, this is not appropriate.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

Adverse events and the associated costs were not included in the model. Therefore, this is not appropriate.

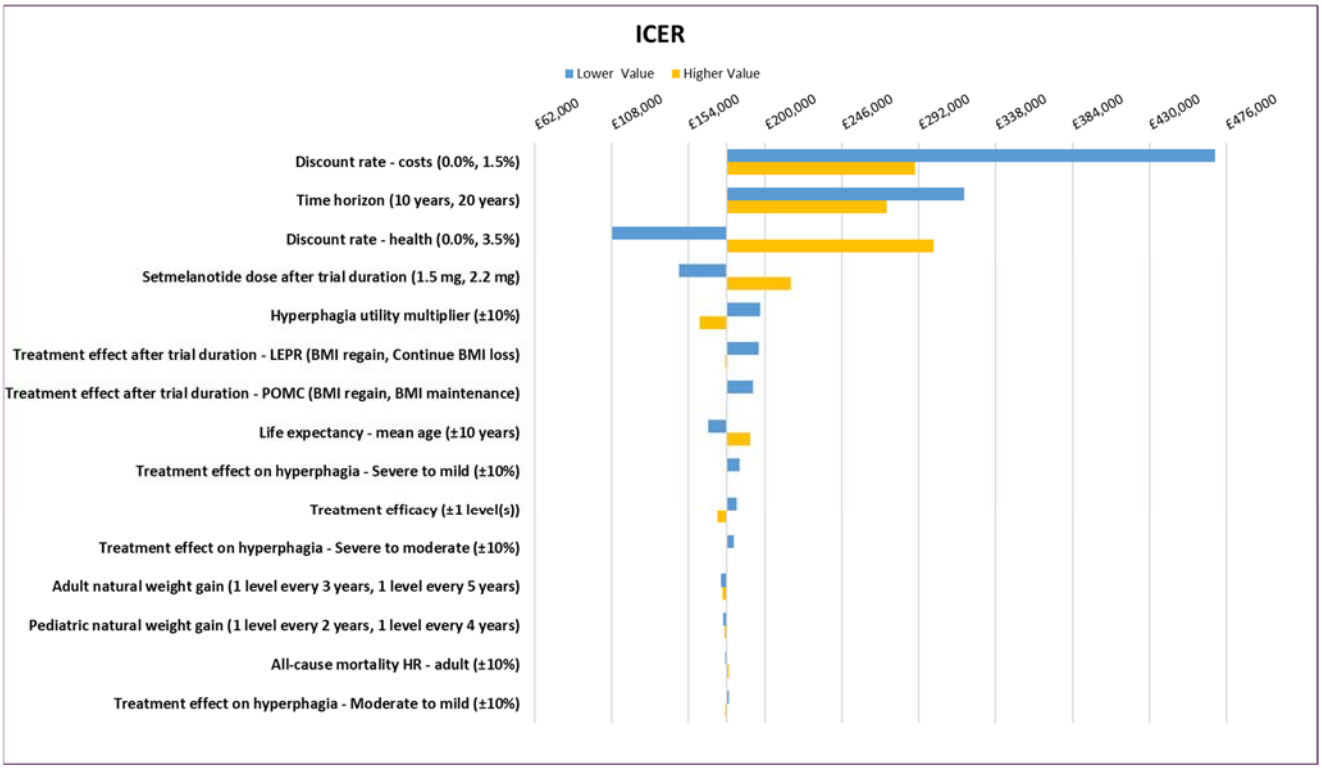
Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in Table 86.

The results of the deterministic sensitivity analysis are presented in .

Figure **26**.

Figure 26 Tornado diagram of one-way sensitivity analysis results



As shown in .

Figure **26**, the primary drivers of model outcomes (defined as parameter values in which changes cause ICER to change by >25% of base case value) are the discount rate for costs, time horizon, and discount rate for health. Secondary drivers (defined as parameter values in which changes cause ICER to change by between 10% and 25% of the base case value) include the dose of setmelanotide after one-year (the trial duration), treatment effect after one-year, the hyperphagia utility, and the mean life expectancy of patients. All other model parameter values impact the ICER by <10%.

Results of the scenario analysis outlined in section 2.4.3 are presented in Table 92 below.

Table 92 Scenario Analysis results

Scenarios	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£) Incremental (QALYs)
Base case	[redacted]	[redacted]	[redacted]	**£176,913**
Scenario 1: Uniform baseline BMI distribution	[redacted]	[redacted]	[redacted]	£173,856
Scenario 2: Distribution of POMC and LEPR based on trial population	[redacted]	[redacted]	[redacted]	£180,010
Scenario 3: Distribution of paediatric and adults based on trial population	[redacted]	[redacted]	[redacted]	£178,696
Scenario 4: All responders have 1 level improvement in hyperphagia	[redacted]	[redacted]	[redacted]	£191,812
Scenario 5: Inclusion of only comorbidities that are prevalent in paediatric subjects	[redacted]	[redacted]	[redacted]	£176,697
Scenario 6: Incremental cost of BSC by BMI	[redacted]	[redacted]	[redacted]	£176,906
Scenario 7: Response rate stratified by age group based on trial	[redacted]	[redacted]	[redacted]	£177,015

Scenario 8: Hyperphagia mapping based on worst hunger score	[redacted]	[redacted]	[redacted]	£224,778
Scenario 9: Increased comorbidity disutility by 50%	[redacted]	[redacted]	[redacted]	£177,134
Scenario 10: Account for acute cost of CV events	[redacted]	[redacted]	[redacted]	£176,929
Scenario 11: Utility scores decreased by 0.05 for BMI ≥ 50	[redacted]	[redacted]	[redacted]	£176,708

Abbreviations: BMI = body mass index; BSC = best supportive care; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; LEPR = leptin receptor; LY = life year; NHS = National Health Service; POMC = pro-opiomelanocortin; QALY = quality-adjusted life year

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in Table 87.

Not applicable

12.5.13 Present results of the probabilistic sensitivity analysis described in Table 88.

Figure 27 Graphical depiction of probabilistic sensitivity analysis results

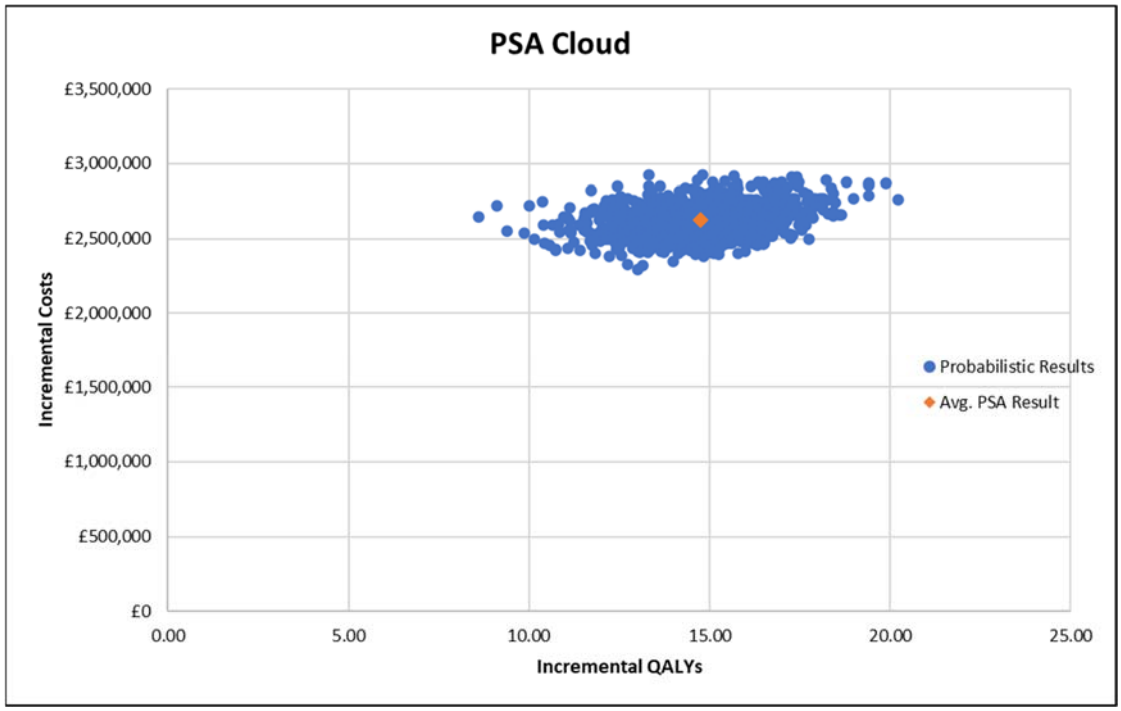
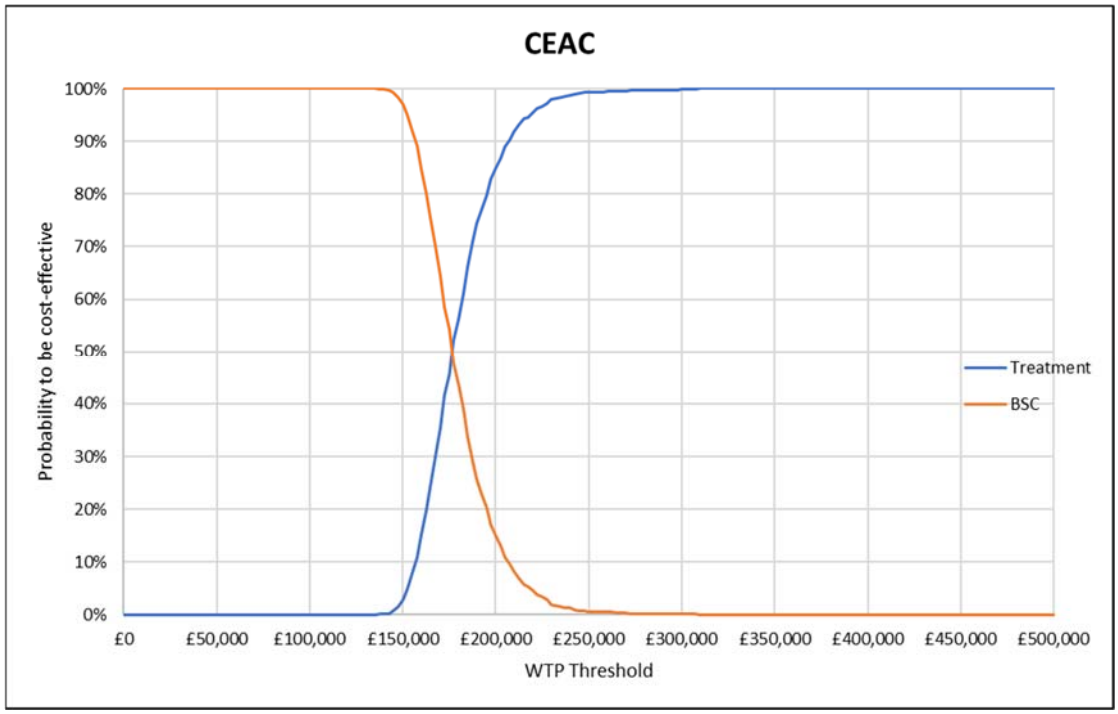


Figure 28 Cost-effectiveness acceptability curve



12.5.14 What were the main findings of each of the sensitivity analyses?

Deterministic, probabilistic and scenario analyses demonstrated that the economic results are robust to changes to key model parameters. The key drivers are discussed in section 12.5.15. The ICER and QALYs vary as expected as model inputs are varied. QALY gains were greater than 11 in 98.4% of PSA scenarios. Furthermore, setmelanotide is associated with substantial QALY gain (> 11) in all scenarios as seen in Table 92. he cost-effectiveness acceptability curve exhibited a steep and definitive switch to setmelanotide becoming more cost-effective than BSC at a WTP threshold of ~£177,000 per QALY gained.

12.5.15 What are the key drivers of the cost results?

As shown in **Error! Reference source not found.**, the primary drivers of model outcomes are the discount rate applied to treatment costs and health and the annual cost of setmelanotide. Secondary drivers of model outcomes include the trajectory of response after one year, the dose of setmelanotide given after one year, and the utility associated with hyperphagia. BMI regain after trial duration in responders, life expectancy in LEPR and POMC/PCSK1

subjects, and treatment efficacy have relatively limited impact on the results compared to the primary and secondary drivers noted above.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None. Results from scenario analyses conducted were described together with one-way sensitivity analysis results in Section 12.5.11 (see Table 92).

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Subgroup analyses were conducted to explore the impact of setmelanotide in four specific subgroups: paediatric with LEPR deficiency, adult with LEPR deficiency, paediatric with POMC/PCSK1 deficiency, adult with POMC/PCSK1 deficiency. No subgroups were specified in the decision problem; however, the population of interest includes the following, which are consistent with the above subgroups:

- People aged 18 and over: BMI 30 kg/m2 and over (adult subjects with obesity)

- People aged 17 and under: weight 97th percentile or more for age on growth chart assessment (paediatric subjects with obesity)

12.6.2 Define the characteristics of patients in the subgroup(s).

The patient subgroups were defined in the model to be consistent with the patients in the setmelanotide Phase III trials of LEPR-deficient and POMC/PCSK1-deficient subjects (NCT03287960 and NCT02896192 and, respectively). Key characteristics of patient subgroups are provided below in Table 93.

Table 93 Key Characteristics of Patient Subgroups

	POMC/PCSK1		LEPR	
	Pediatric	**Adults**	**Pediatric**	**Adults**
Mean age (years)	13	25	12	26
Sex (% female)	33.3%	40.0%	60.0%	60.0%

Abbreviations: LEPR = leptin receptor; POMC = pro-opiomelanocortin;

12.6.2.1 ***Describe how the subgroups were included in the cost-effectiveness analysis.***

12.6.3 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

The discounted cost-effectiveness results from subgroup analyses are presented in Table 94 below. Additionally, the undiscounted results from the same analyses are presented in Table 95 below. These results are based on four individual cohorts comprising of paediatric patients with LEPR deficiency, adult patients with LEPR deficiency, paediatric patients with POMC/PCSK1 deficiency, and adult patients with POMC/PCSK1 deficiency as described above.

Table 94 Subgroup analyses results - discounted

Subgroup	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Incremental (QALYs)
Setmelanotide + BSC, Paediatric LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,424
BSC, Paediatric LEPR	£28,089	14.21	3.30	-	-	-	-
Setmelanotide + BSC, Paediatric POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£191,348
BSC, Paediatric POMC	£43,104	23.86	7.03	-	-	-	-
Setmelanotide + BSC, Adult LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£181,769
BSC, Adult LEPR	£17,103	5.75	1.12	-	-	-	-
Setmelanotide + BSC, Adult POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,100
BSC, Adult POMC	£34,638	15.82	4.43	-	-	-	-

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Table 95 Subgroup analyses results - undiscounted

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) Incremental (QALYs)
Setmelanotide + BSC, Paediatric LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£270,154
BSC, Paediatric LEPR	£40,337	16.59	3.67	-	-	-	-
Setmelanotide + BSC, Paediatric POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£300,050
BSC, Paediatric POMC	£74,602	30.50	8.47	-	-	-	-
Setmelanotide + BSC, Adult LEPR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£284,997
BSC, Adult LEPR	£20,805	6.27	1.16	-	-	-	-
Setmelanotide + BSC, Adult POMC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£278,623
BSC, Adult POMC	£50,637	18.79	4.99	-	-	-	-

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

12.6.4 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

No subgroups of specified interest to the decision problem were excluded from the analysis.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model was quality checked, validated internally by a senior health economist to ensure technical accuracy of all calculations, and subjected to extreme value testing to ensure overall robustness of model behaviors.

Due to a paucity of evidence in LEPR and POMC/PCSK1-deficient subjects, formal cross-validation of model results by comparison to published evidence was generally not possible. However, in specific instances (e.g., treated and untreated lifespan estimates / mortality), expert opinion provided direct estimates of the expected lifespan of subjects who have received treatment with setmelanotide (8). These estimates were then used to determine mortality distributions used in the model. Also, where possible, published evidence was used to directly inform the model. For example, evidence from pivotal trials of setmelanotide were used directly to inform treatment effect after one year in responder and non-responder patients.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No prior cost-effectiveness analysis is published in the literature for individuals with obesity associated with LEPR and POMC/PCSK1 deficiencies. Results from published economic literature for treatment in general obesity population such as orlistat, methylcellulose, and bariatric surgery are not relevant as they are not effective in individuals with obesity associated with LEPR and POMC/PCSK1 deficiencies.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes, the economic analysis was conducted in adults and children with obesity associated with LEPR or POMC/PCSK1 deficiencies aged six years old and above. A set of subgroup analysis was also conducted to explore the impact of setmelanotide in four specific subgroups: paediatric with LEPR deficiency, adult with LEPR deficiency, paediatric with POMC/PCSK1 deficiency, adult with POMC/PCSK1 deficiency.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strengths of this analysis are as follows:

- Despite the very limited data characterizing the patient populations of interest, the model structure captures the key elements of the natural history of obesity related to LEPR and POMC/PCSK1 deficiency and response to treatment that are most relevant to the economic value of setmelanotide. These include, but are not limited to, the effect of BMI change on mortality and risk of obesity-related comorbidities, correction of the defective MCR4 axis and reduced hyperphagia, quality of life impact of obesity-related comorbidities.

- Major data gaps are addressed using the opinion of UK-based clinicians with expertise in obesity, including a renowned expert in the treatment of patients with obesity associated with LEPR and POMC/PCSK1 deficiency, who was able to provide real-world evidence not available either through publication or other sources.

- The model can be used to study the impact of treatment of obesity associated with LEPR and POMC/PCSK1 deficiencies from early childhood to adulthood and end of life.

- The model explicitly accounts for the utility related to hyperphagia according to severity (mild, moderate, severe), thereby enabling reductions in hyperphagia, a key and unique effect of setmelanotide, to be more accurately captured than in previously used approaches.

- The model accounts for very high BMI and BMI Z-score health states to better capture the economic and clinical aspects of patients with LEPR and POMC/PCSK1 deficiencies that often include individuals with extremely high BMI.

- The model considers the economic impact of reducing the complications of obesity that are of primary relevance in the LEPR and POMC/PCSK1-deficient populations, according to clinical experts in the treatment of such patients.

The weaknesses of this analysis are as follows:

- Due to lack of patient level data or published evidence on key clinical and economic inputs for individuals with obesity associated with LEPR and POMC/PCSK1 deficiencies, the input parameter values in the model were mainly informed from published literature on the general obesity population, patients eligible for bariatric surgery, and clinical expert opinion.

- The model can only capture the mean annual cost and disutility for obesity related complications, as prevalence rates were used to estimate the number of patients with different complications during each model cycle.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Most of the major challenges in developing the economic evaluation of setmelanotide arose from the substantial material data gaps related to patients with obesity arising from LEPR or POMC/PCSK1 deficiency, particularly related to the lifespan of both untreated subjects and those treated with setmelanotide and the resolution of obesity-related comorbidities in treated subjects. Having access to retrospective real-world data or mature clinical trial data from long-term extension studies that characterize these phenomena would be the ideal way to enhance the robustness of results; however, neither option is currently feasible.

Due to these data gaps, in surrogate indication data from general obesity and/or the opinion of clinical experts were used to inform parameter value estimates in the model where required. Care was taken to ensure that the impact of the parameter values derived from these estimates and to which the model behaviours were most sensitive as identified by the OWSA were thoroughly assessed. Two methods were employed:

- Scenario analyses compared differences between evidence from general obesity and the opinion of clinical experts (e.g., general obesity utility scores for sleep apnoea vs. LEPR and POMC/PCSK1 deficiency)
- Exploration of expanded ranges of the parameter values in the PSA beyond the standard ranges (e.g., for treatment-based lifespan extension / mortality estimates)

These analyses showed that the model was relatively insensitive to many of the material evidence gaps and suggest that access to these data, while potentially helpful to refine the model, will not substantially change the economic value story.

13 Cost to NHS and Personal Social Services

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

It is not possible to determine the exact number of patients in England with POMC/PCSK1 or LEPR deficiency. Based on current epidemiology data we estimate the maximum number of POMC/PCSK1/LEPR patients combined to be 100, however, the leading KOL believes the true number to be around [redacted] cases, with this number possibly rising to [redacted] based on the assumption that more genetic testing may be carried out once a treatment for the condition is available. For the purposes of estimating the budget impact we have assumed [redacted] patients are eligible in year 1, rising to [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5. These numbers are likely to be an overestimate.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

It is expected that the majority of patients identified as having POMC/PCSK1 or LEPR deficiency will be started on setmelanotide as it will be the only available treatment and demand is therefore expected to stay stable over the next 5 years. There may be a slight increase in the numbers of patients identified based on the assumption that currently some patients are not being referred for genetic testing due to there being no available treatment option, however KOL opinion is that the majority of suspected cases are currently referred for testing.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

All patients who receive setmelanotide must have confirmation of POMC/PCSK1 or LEPR deficiency via a genetic test. This test is already being funded by NHS England so would not be an additional cost associated with the use of setmelanotide.

13.4 Describe any estimates of resource savings associated with the use of the technology.

N/A

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is reasonable to hypothesize that children who receive setmelanotide treatment in childhood and do not go on to become obese will avoid the future comorbidities and resultant resource use associated with obesity. For example, T2DM medication, surgery for joint and mobility problems resulting from excess weight on the developing child skeleton, CPAP or BiPAP for sleep apnoea.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Patients with genetic obesity report their obesity has an impact on their ability to study and work. The work prospects of children and adults who are treated with setmelanotide may therefore improve. Likewise, parents'/carers' ability to work can be impaired by having to care for their child with genetic obesity and their mental health can suffer.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Table 96 Technology budget impact analysis over the next five years

	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Setmelanotide annual list price per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Proposed list price by manufacturer and assumed average dose of [redacted] mg/day
Supportive annual treatment cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual Gross treatment cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Based on proposed list price
Cost of displaced treatments per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual net treatment cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Based on proposed list price
Eligible patients (if 100% identified and genotyped)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Based on current internal epidemiology data (2)
Cumulative number of identified and genotyped patients (biallelic LoF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Based on UK clinical expert (8)
Initial uptake rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Based on UK clinical expert (8)
Converting to maintenance treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pivotal trial data (86, 87)
Number of patients treated (chronic treatment) – Patient years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
Number of patients (induction period 12 weeks) – Patient years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
Total number of patient years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
Other savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Conservative assumption
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: LoF = loss of function

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The exact number of patients who are likely to be identified as being eligible for setmelanotide is unknown. It is likely that the actual number of patients identified each year is less the numbers used in the model (the leading KOL estimates approximately 12 patients).

Section E – Impact of the technology beyond direct health benefits

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services or are associated with significant benefits other than health.

Most of the costs and health outcomes relevant to the decision problem are captured within the economic analysis. Costs associated with management of obesity linked to LEPR and POMC deficiency are typically born by the NHS. However, obesity also causes a significant burden beyond the healthcare sector. A Public Health England report published in 2017 estimated that the overall cost of obesity of all causes to wider society was £27 billion (120).

RDGOs, such as LEPR and POMC deficiency, often result in the onset of obesity in infancy and the period of children's social development. Obese children are more likely to be bullied compared with their normal weight peers, which may result in reduced self-esteem and poorer educational attainment, ultimately affecting lifetime achievement (121).

Hyperphagia can constrain patients' lives with constant food seeking behaviour impacting the ability to study or work. Caregivers can also be affected by this behaviour, especially if they are required to provide constant supervision to regulate food intake. This can have a significant impact on caregivers' mental health and the parent/child relationship. Caregivers may also need to give up work, or work part time, to enable them to care for the child.

In adults, obesity is associated with work absenteeism and presenteeism as well as permanent work loss (25). Employed obese people generally have significantly higher indirect costs (absenteeism, short- and long-term disability etc.) compared with employed normal weight people. An EU5 study into the humanistic and economic burden of increasing body mass index found that obese respondents had significantly greater absenteeism and presenteeism

than normal weight respondents and calculated that those employed respondents with a BMI ≥40 kg/m that amounted to almost €2,000 more in indirect costs (122). 1.2 List the costs (or cost savings) to government bodies other than the NHS.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Given the strongly debilitating nature of obesity due to LEPR and POMC deficiency, children with this condition are likely to require additional support at school. In the UK, governing bodies must ensure that all children with medical conditions, in terms of both physical and mental health, are properly supported at school and have full access to education so that they can remain healthy and achieve their full academic potential (123). Schools, local authorities, health professionals, commissioners and other support services should work together to ensure that children with medical conditions receive a full education. In some cases, this will require flexibility and involve, for example, programmes of study that rely on part-time attendance at school in combination with alternative provision arranged by the local authority. The organisation and logistics of these education and social services may entail some additional resources and costs. Other costs to government bodies other than the NHS may include disability and other welfare payments linked to adult patients' inability to work.

Depending on the severity of their obesity, some patients may be eligible for a Personal Independence Payment (PIP) if they are aged 16 or over and have not reached State Pension age. The amount of disability support depends on how the condition affects the patient, not the condition itself. A healthcare professional is responsible for determining the level of help a patient can claim (124).

14.3 List the costs borne by patients that are not reimbursed by the NHS.

The main costs incurred by patients and carers are the cost of travelling to and from appointments. To be seen by a specialist, obese patients have to be referred by their GP to a specialised obesity service (tier 2 service). Specialised obesity service appointments take place at Cambridge and some patients may have to travel a significant distance to get there. In some

instances, an overnight stay may be necessary, which is associated with additional costs not reimbursed by the NHS. In addition, given the involvement of hyperphagia in both POMC and LEPR deficiencies, it is a fair assumption that these patients or their carers will spend significantly more on food than normal weight counterparts.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

There are no studies which evaluate the time spent by family members providing care for patients with obesity associated with LEPR and POMC mutations. However, given the severity of the condition and the complications associated with it, it would be reasonable to assume that one of the parents may have to work part-time or even give up on their job due to the care they need to provide to their children.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The Genetics of Obesity Study (GOOS) was established to elucidate the variability in weight across people and understand why some people put on weight more easily than others. There are hundreds of genes that regulate weight and tracking them down is complicated. Finding the genes that influence weight the most is a key mechanism to understand how weight is regulated. The GOOS study has recruited more than 7800 adults and children with severe, early-onset obesity, defined as BMI SDS > 3 before 10 years of age (125). The study screens patients using a 41-gene panel for mutations in some highly penetrant genes, which are likely to have an effect in the development or predisposition to obesity. Once scientists discover a gene that is likely to be the cause of someone's weight problem, they investigate the whole neuronal and biochemical pathways associated with these genes to find how these mutations can be managed therapeutically. Setmelanotide has already been initiated on some of the patients involved in the GOOS study providing valuable insights into the MC4R pathway and genetic obesity in general.

14.6 **Describe the anticipated impact of the technology on innovation in the UK.**

There are currently no approved treatments indicated specifically for the treatment of obesity due to LEPR and POMC deficiency. Setmelanotide will be the only pharmacotherapy indicated for chronic weight management in adult and paediatric patients 6 years of age and older with obesity due to LEPR or POMC deficiency confirmed by genetic testing demonstrating variants in the LEPR or POMC genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (Refer to Section B, section 3.5). Up to this moment patients with these RDGOs have been treated for general obesity without targeting the underlying cause of the condition and specifically the hyperphagia that leads to obesity. Setmelanotide is innovative in that it is the first pharmacological treatment that treats hyperphagia by targeting the dysfunctional MC4R pathway in patients with LEPR and POMC deficiency, which results in a decrease in their hunger level and consequently a reduction in their body weight. Setmelanotide is therefore an opportunity for the UK to embrace a truly innovative technology with the potential to have a significant impact on both the quantity and quality of life of patients who have previously been stigmatised for what was seen as a 'lifestyle' issue.

14.7 **Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.**

A PASS+ registry is currently being discussed with EMA. The registry of patients will be implemented to:

- Assess the long-term safety of setmelanotide as prescribed in routine practice for patients with biallelic homozygous LEPR or POMC deficiency obesity according to the current local prescribing information
- Document the incidence and characteristics of adverse events of special interest (AESI) including the following:
- Document AESI and new adverse event (AE) occurrence in special populations

The registry will be conducted at centres prescribing setmelanotide in routine practice in at least five European countries and the United States (US).

- The enrolment period will be four years from the earliest setmelanotide market entry date.
- The study period will be nine years from the earliest setmelanotide market entry.
- Patients will be followed up until four months after the end of setmelanotide treatment, loss to follow-up, death or end of study period, whichever comes first.
- Current users (continuing treatment from an open-label, long-term follow-up or from an early access programme) will also be included, and the registry follow-up will add to any previous follow-up time.

The list of study countries will be revised according to market uptake after the setmelanotide launch and could include other European Union (EU) countries, if necessary.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

To review setmelanotide's ongoing clinical effectiveness in clinical practice data will continue to be collected at Addenbrooke's Hospital, providing appropriate real-world evidence (RWE) of relevant outcomes in patients diagnosed with obesity associated with LEPR/POMC deficiency who receive the drug. As part of the regulatory processes, the manufacturer will have to set up an international patient registry that will collect RWE on safety and efficacy for setmelanotide. It is anticipated that the data collection at Addenbrooke's Hospital will be incorporated within the international patient registry.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

It is anticipated that setmelanotide will be initiated at a National Expert Centre, given the requirement for a genetic test to confirm the presence of POMC or LEPR deficiency. All treatment decisions would be made by the national expert, with the patient referred back to local centres for maintenance treatment.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure to that which is already in operation will be required. Confirmation of the specific genetic cause of obesity will be required via genetic testing, however this is already being implemented in the NHS. Increased awareness of potential genetic causes of obesity, particularly in very young patients with high weight gain trajectory will be necessary to ensure all patients who might benefit from setmelanotide treatment are offered it.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

The manufacturer will not propose a complex managed access arrangement. Therefore, this section is not applicable.

16 References

1. Poitou C, Puder L, Dubern B, Krabusch P, Genser L, Wiegand S, et al. Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes. Surgery for Obesity and Related Diseases. 2021.

2. file Do.

3. van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell. 2015;161(1):119-32.

4. Kleinendorst L, van Haelst MM, van den Akker EL. Genetics of obesity. Genetics of Endocrine Diseases and Syndromes. 2019:419-41.

5. (NHS) NHS. Obesity Overview 2021 [Available from: https://www.nhs.uk/conditions/obesity/.

6. Excellence NIoHaC. Clinical guideline [CG189] Obesity: identification, assessment and management NICE webpage: NICE; 2014 [Available from: https://www.nice.org.uk/guidance/cg189.

7. Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. Journal of Endocrinology. 2014;223(1):T63-T70.

8. Farooqi. Personal communication.

9. Heymsfield SB, Avena NM, Baier L, Brantley P, Bray GA, Burnett LC, et al. Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia. Obesity. 2014;22(S1):S1-S17.

10. Fairbrother U, Kidd E, Malagamuwa T, Walley A. Genetics of severe obesity. Current diabetes reports. 2018;18(10):1-9.

11. Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? Jama. 2014;311(21):2167-8.

12. Shen W-j, Yao T, Kong X, Williams KW, Liu T. Melanocortin neurons: Multiple routes to regulation of metabolism. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017;1863(10):2477-85.

13. Fani L, Bak S, Delhanty P, Van Rossum E, Van Den Akker E. The melanocortin-4 receptor as target for obesity treatment: a systematic review of emerging pharmacological therapeutic options. International journal of obesity. 2014;38(2):163-9.

14. Seidah NG, Prat A. The biology and therapeutic targeting of the proprotein convertases. Nature reviews Drug discovery. 2012;11(5):367-83.

15. Coll AP, Farooqi IS, Challis BG, Yeo GS, O'Rahilly S. Proopiomelanocortin and energy balance: insights from human and murine genetics. The Journal of Clinical Endocrinology & Metabolism. 2004;89(6):2557-62.

16. Ramachandrappa S, Farooqi IS. Genetic approaches to understanding human obesity. The Journal of clinical investigation. 2011;121(6):2080-6.

17. Challis B, Millington G. Proopiomelanocortin deficiency. 2013.

18. Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obes Facts. 2016;9(3):158-73.

19. da Fonseca ACP, Mastronardi C, Johar A, Arcos-Burgos M, Paz-Filho G. Genetics of non-syndromic childhood obesity and the use of high-throughput DNA sequencing technologies. Journal of diabetes and its complications. 2017;31(10):1549-61.

20. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. New England Journal of Medicine. 2007;356(3):237-47.

21. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health. 2009;9(1):1-20.

22. Narang I, Mathew JL. Childhood obesity and obstructive sleep apnea. Journal of nutrition and metabolism. 2012;2012.

23. Selvakumar PKC, Kabbany MN, Alkhouri N. Nonalcoholic fatty liver disease in children: not a small matter. Pediatric Drugs. 2018;20(4):315-29.

24. Aykut A, Özen S, Gökşen D, Ata A, Onay H, Atik T, et al. Melanocortin 4 receptor (MC4R) gene variants in children and adolescents having familial early-onset obesity: genetic and clinical characteristics. European journal of pediatrics. 2020:1-8.

25. Goettler A, Grosse A, Sonntag D. Productivity loss due to overweight and obesity: a systematic review of indirect costs. BMJ open. 2017;7(10):e014632.

26. Nigatu YT, Bültmann U, Reijneveld SA. The prospective association between obesity and major depression in the general population: does single or recurrent episode matter? BMC Public Health. 2015;15(1):1-8.

27. Clément K, Biebermann H, Farooqi IS, Van der Ploeg L, Wolters B, Poitou C, et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. Nature medicine. 2018;24(5):551-5.

28. Kleinendorst L, Abawi O, van der Kamp HJ, Alders M, Meijers-Heijboer HE, van Rossum EF, et al. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. European journal of endocrinology. 2020;182(1):47-56.

29. (EMA) EMA. Setmelanotide - Orphan Drug Designation for the Treatment of Leptin Receptor Deficiency: EMA; 2018 [Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182101.

30. (EMA) EMA. Setmelanotide - Orphan Drug Designation for the Treatment of Pro-opiomelanocortin Deficiency EMA webpage2016 [Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161703.

31. Hilbert A, Rief W, Braehler E. Stigmatizing attitudes toward obesity in a representative population-based sample. Obesity. 2008;16(7):1529-34.

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

33. Estrada E, Knox J, Reed C, Hadker N, Fay M, McCagg A. PDB109 BURDEN OF ILLNESS ASSOCIATED WITH HYPERPHAGIA AND SEVERE OBESITY. Value in Health. 2019;22:S592.

34. Fehnel S. Qualitative Interviews With Setmelanotide Trial Participants. RTI Health Solutions; 2021.

35. santé HAd. Overweight and obesity in adults: primary care medical management. 2011.

36. P C. Regards croisés entre médecins et patients. Humanities and Social Sciences. Sociology speciality; 2015.

37. High Authority for Health FH. Overweight and obesity in children and adolescents. 2011.

38. Kolotkin RL, Binks M, Crosby RD, Østbye T, Gress RE, Adams TD. Obesity and sexual quality of life. Obesity. 2006;14(3):472-9.

39. Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obesity. 2009;17(5):941.

40. Puhl RM, Andreyeva T, Brownell KD. Perceptions of weight discrimination: prevalence and comparison to race and gender discrimination in America. International journal of obesity. 2008;32(6):992-1000.

41. Genentech. XENICAL (orlistat) US Prescribing Information: FDA; 2015 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020766s035lbl.pdf.

42. VIVUS. QSYMIA (phentermine and topiramate extended-release) US Prescribing Information: QSYMIA webpage; 2018 [Available from: https://qsymia.com/hcp/include/media/pdf/prescribing-information.pdf.

43. Pharmaceuticals C. CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) US Prescribing Information FDA webpage: FDA; 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/200063s015lbl.pdf.

44. Nordisk N. SAXENDA (liraglutide) US Prescribing Information FDA webpage: FDA; 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206321s011lbl.pdf.

45. Excellence NIoHaC. NICE guideline [NG7] Preventing excess weight gain NICE webpage: NICE; 2015 [Available from: https://www.nice.org.uk/guidance/ng7.

46. Excellence NIoHaC. Clinical guideline [CG43]. Obesity prevention NICE webpage: NICE; 2006 [Available from: https://www.nice.org.uk/guidance/cg43.

47. Golubic R, Laur C, Kelsey M, Livesy A, Hoensch J, Park A, et al. The Cambridge intensive weight management programme appears to promote weight loss and reduce the need for bariatric surgery in obese adults. Frontiers in nutrition. 2018;5:54.

48. Kohlsdorf K, Nunziata A, Funcke J-B, Brandt S, von Schnurbein J, Vollbach H, et al. Early childhood BMI trajectories in monogenic obesity due to leptin, leptin receptor, and melanocortin 4 receptor deficiency. International Journal of Obesity. 2018;42(9):1602-9.

49. Choquet H, Meyre D. Genomic insights into early-onset obesity. Genome medicine. 2010;2(6):1-12.

50. Norris T, Cole TJ, Bann D, Hamer M, Hardy R, Li L, et al. Duration of obesity exposure between ages 10 and 40 years and its relationship with cardiometabolic disease risk factors: A cohort study. PLoS medicine. 2020;17(12):e1003387.

51. Dankel SJ, Loenneke JP, Loprinzi PD. Health outcomes in relation to physical activity status, overweight/obesity, and history of overweight/obesity: a review of the WATCH paradigm. Sports Medicine. 2017;47(6):1029-34.

52. Pharmaceuticals R. IMCIVREE (setmelanotide) US Prescribing Information FDA webpage: FDA; 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213793s000lbl.pdf.

53. England N. National Genomic Test Directory. Testing Criteria for Rare and Inherited Disease. 2020.

54. Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. N Engl J Med. 2016;375:240-6.

55. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol. 2020;8(12):960-70.

56. file Do. Rhythm Pharmaceuticals Clinical Study Reports.

57. Onis Md, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World health Organization. 2007;85:660-7.

58. Ells LJ, Rees K, Brown T, Mead E, Al-Khudairy L, Azevedo L, et al. Interventions for treating children and adolescents with overweight and obesity: an overview of Cochrane reviews. International Journal of Obesity. 2018;42(11):1823-33.

59. Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, et al. Screening for thyroid cancer: US Preventive Services Task Force recommendation statement. Jama. 2017;317(18):1882-7.

60. Wiegand S, Keller K-M, Lob-Corzilius T, Pott W, Reinehr T, Röbl M, et al. Predicting weight loss and maintenance in overweight/obese pediatric patients. Hormone research in paediatrics. 2014;82(6):380-7.

61. Kirk S, Zeller M, Claytor R, Santangelo M, Khoury PR, Daniels SR. The relationship of health outcomes to improvement in BMI in children and adolescents. Obesity research. 2005;13(5):876-82.

62. TM P. Pediatric Quality of Life Inventory TM [Available from: https://www.pedsql.org/.

63. IWQOL-Lite. Assessing the impact of weight on quality of life in adults [Available from: https://www.qualityoflifeconsulting.com/iwqol-lite.html.

64. Kroes M, Osei-Assibey G, Baker-Searle R, Huang J. Impact of weight change on quality of life in adults with overweight/obesity in the United States: a systematic review. Current medical research and opinion. 2016;32(3):485-508.

65. Warkentin LM, Majumdar SR, Johnson JA, Agborsangaya CB, Rueda-Clausen CF, Sharma AM, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. BMC medicine. 2014;12(1):1-9.

66. Hainerová IA, Lebl J. Treatment options for children with monogenic forms of obesity. Nutrition and Growth. 2013;106:105-12.

67. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity—assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2017;102(3):709-57.

68. Jia H, Lubetkin EI. The impact of obesity on health-related quality-of-life in the general adult US population. Journal of public health. 2005;27(2):156-64.

69. Jagielski AC, Brown A, Hosseini-Araghi M, Thomas GN, Taheri S. The association between adiposity, mental well-being, and quality of life in extreme obesity. PloS one. 2014;9(3):e92859.

70. Nigatu YT, Reijneveld SA, de Jonge P, van Rossum E, Bültmann U. The combined effects of obesity, abdominal obesity and major depression/anxiety on health-related quality of life: the lifelines cohort study. PloS one. 2016;11(2):e0148871.

71. Riazi et al. Based on PedsQoL at early to post pubertal stage. 2010.

72. Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014;32(7):693-706.

73. Alsumali et al. SF-12 data taken from the MEPS general population mapped to EQ-5D 2018.

74. Søltoft F, Hammer M, Kragh N. The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Quality of life research. 2009;18(10):1293-9.

75. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical Decision Making. 2011;31(6):800-4.

76. National Guideline Centre (UK). Non-Alcoholic Fatty Liver Disease: Assessment and Management. Appendix N, Cost-effectiveness analysis: diagnostic tests for NAFLD and advanced fibrosis. London: National Institute for Health and Care Excellence (UK); 2016.

77. National Institute for Health and Care Excellence. Obesity: identification, assessment and management. Clinical guideline [CG189]2014.

78. Brandt S, von Schnurbein J, Lennerz B, Kohlsdorf K, Vollbach H, Denzer C, et al. Methylphenidate in children with monogenic obesity due to LEPR or MC4R deficiency improves feeling of satiety and reduces BMI-SDS-A case series. Pediatr Obes. 2020;15(1):e12577.

79. Aslan IR, Ranadive SA, Valle I, Kollipara S, Noble JA, Vaisse C. The melanocortin system and insulin resistance in humans: insights from a patient with complete POMC deficiency and type 1 diabetes mellitus. International journal of obesity (2005). 2014;38(1):148-51.

80. Poitou et al. Surg. For Obesity and Related Diseases. 2021.

81. Kleinendorst L, van Haelst MM, van den Akker ELT. Genetics of Obesity. Exp Suppl. 2019;111:419-41.

82. Excellence NIfHaC. Liraglutide for managing overweight and obesity

Technology appraisal guidance [TA664]. 2020.

83. Excellence NIfHaC. Naltrexone–bupropion for managing overweight and obesity

Technology appraisal guidance [TA494]. 2017.

84. Excellence NIfHaC. Rimonabant for the treatment of overweight and obese adults

Technology appraisal guidance [TA144]. 2008.

85. Excellence NIfHaC. Metreleptin for treating lipodystrophy

Highly specialised technologies guidance [HST14]. 2021.

86. ClinicalTrials.gov. Setmelanotide for the Treatment of LEPR Deficiency Obesity. In: Rhythm Pharmaceuticals I, editor. 2017.

87. ClinicalTrials.gov. Setmelanotide for the Treatment of Early-Onset POMC Deficiency Obesity. In: Rhythm Pharmaceuticals I, editor. 2016.

88. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Archives of disease in childhood. 1995;73(1):25-9.

89. Wilding J. Personal communication.

90. World Health Organization. Computation of Centiles and Z-Scores for Height-for-Age, Weight-for-Age amd BMI-for-Age.

91. Excellence NIfHaC. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017.

92. EXCELLENCE NIFHAC. CHTE methods review. 2020.

93. National Institute for Health and Care Excellence. Mifamurtide for the treatment of osteosarcoma. Technology appraisal guidance [TA235]2011.

94. Ara and Brazier Value Health. 2010.

95. Office for National Statistics. National life tables: UK. 2020.

96. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol. 2018;6(12):944-53.

97. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J. 2000;139(2 Pt 1):272-81.

98. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.

99. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.

100. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217-39.

101. Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation:

more evidence for routine screening for obstructive sleep apnea before weight loss surgery. Am Surg. 2008;74(9):834-8.

102. Ahmad A, Laverty AA, Aasheim E, Majeed A, Millett C, Saxena S. Eligibility for bariatric surgery among adults in England: analysis of a national cross-sectional survey. JRSM Open. 2014;5(1):2042533313512479-.

103. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018;69(4):896-904.

104. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6(12):1396-402.

105. Register ECT. Long Term Extension Trial of setmelanotide (RM-493) 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. 2017 [

106. Graves LE, Khouri JM, Kristidis P, Verge CF. Proopiomelanocortin deficiency diagnosed in infancy in two boys and a review of the known cases. J Paediatr Child Health. 2021;57(4):484-90.

107. Kleinendorst L, Abawi O, van der Kamp HJ, Alders M, Meijers-Heijboer HEJ, van Rossum EFC, et al. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. Eur J Endocrinol. 2020;182(1):47-56.

108. Stijnen P, Ramos-Molina B, O'Rahilly S, Creemers JW. PCSK1 Mutations and Human Endocrinopathies: From Obesity to Gastrointestinal Disorders. Endocr Rev. 2016;37(4):347-71.

109. Argente J, Tatton-Brown K, Lehwalder D, Pfäffle R. Genetics of Growth Disorders-Which Patients Require Genetic Testing? Front Endocrinol (Lausanne). 2019;10:602-.

110. Lesley Curtis AB. Unit Costs of Health and Social Care 2019 2019 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.

111. Burns LCaA. Unit Costs of Health and Social Care 2020 2020 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/.

112. Curtis L BA. Unit costs of health and social care 2017. Canterbury, UK: Personal Social Services Research Unit, University of Kent; 2017.

113. Ara R, Blake L, Gray L, Hernández M, Crowther M, Dunkley A, et al. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review. Health Technol Assess. 2012;16(5):iii-xiv, 1-195.

114. NHS. Reference Costs 2017/2018. 2018.

115. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, et al. A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT. Health Technology Assessment (Winchester, England). 2015;19(40):1.

116. Oxford Economics. The economic costs of arthritis for the UK economy. Final Report. Oxford, UK2010.

117. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577-86.

118. Currie CJ, Poole CD, Woehl A, Morgan CL, Cawley S, Rousculp MD, et al. The financial costs of healthcare treatment for people with Type 1 or Type 2 diabetes in the UK with particular reference to differing severity of peripheral neuropathy. Diabet Med. 2007;24(2):187-94.

119. Danese MD, Gleeson M, Kutikova L, Griffiths RI, Azough A, Khunti K, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ Open. 2016;6(8):e011805.

120. England PH. Guidance: Health matters: obesity and the food environment gov.uk2017 [Available from: https://www.gov.uk/government/publications/health-matters-obesity-and-the-food-environment/health-matters-obesity-and-the-food-environment--2.

121. Dietitians TAoU. Policy Statement. UK Government's Childhood Obesity Strategy. 2018.

122. Gupta S, Richard L, Forsythe A. The humanistic and economic burden associated with increasing body mass index in the EU5. Diabetes, metabolic syndrome and obesity: targets and therapy. 2015;8:327.

123. Education Df. Supporting pupils at school with medical conditions. Statutory guidance for governing bodies of maintained schools and proprietors of academies in England. gov.uk; 2015.

124. UK G. Personal Independence Payment (PIP) 2021 [Available from: https://www.gov.uk/pip.

125. Lawler K, Huang-Doran I, Sonoyama T, Collet T-H, Keogh JM, Henning E, et al. Leptin-mediated changes in the human metabolome. The Journal of Clinical Endocrinology & Metabolism. 2020;105(8):2541-52.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient Access Scheme submission template

May 2019

1 Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (2019 VS) the transition arrangements as set out in paragraph 3.28 state that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the 2019 VS, any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies and sponsors

This document is the Patient Access Scheme submission template for highly specialised technologies. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a highly specialised technologies evaluation, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a highly specialised technologies evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the highly specialised technologies evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies'. The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technologies evaluation, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated.

If you are submitting the Patient Access Scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the highly specialised technology and the disease area to which the Patient Access Scheme applies.

Setmelanotide (IMCIVREE) for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above

3.2 Please outline the rationale for developing the Patient Access Scheme.

The purpose of the Patient Access Scheme is to allow setmelanotide reach the cost-effectiveness threshold set by NICE.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price

Simple discount of [redacted]% on the NHS list price of [redacted] per patient per year.

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS will apply to the whole licensed population.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example,

degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme will apply to all patients who are initiated on setmelanotide.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The entire licenced indicated population is expected to meet the scheme criteria

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The scheme will not involve rebates. The original invoice from the company to the purchasing organisation will show the discount being applied.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

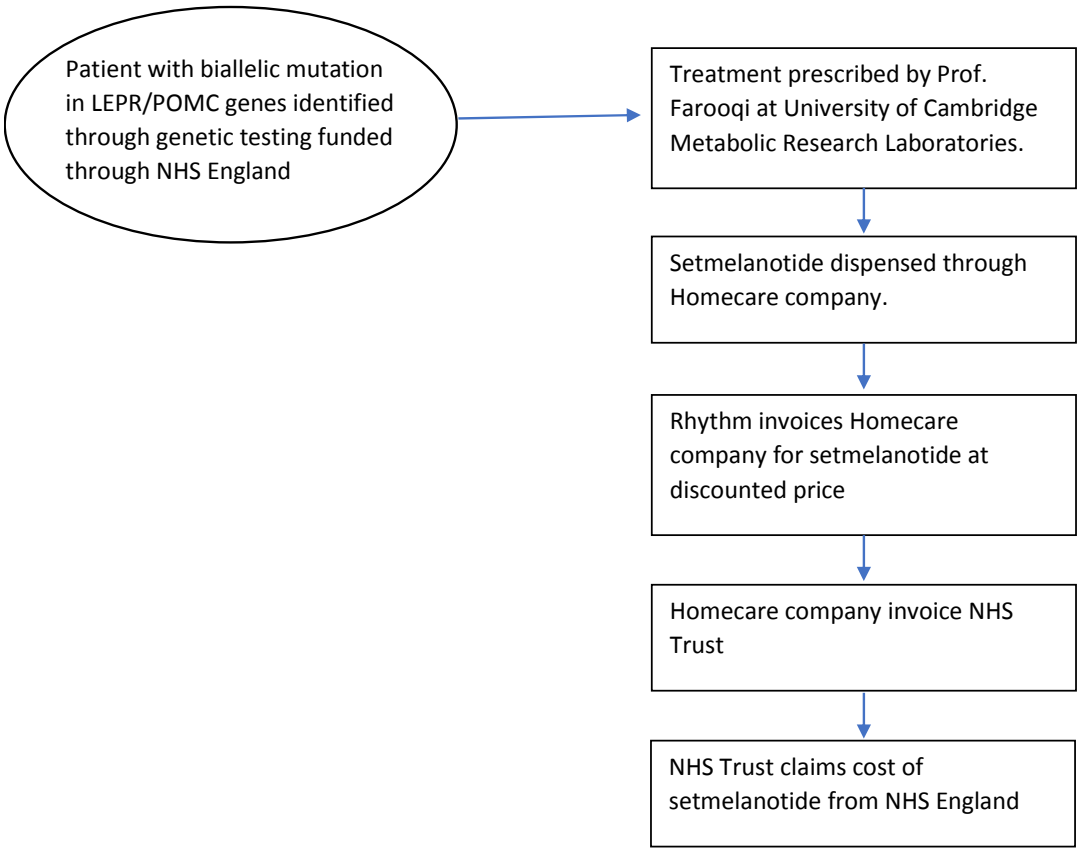
The scheme does not introduce any additional administrative burden over and above the standard requirements for other specialised commissioning products.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

We anticipate that setmelanotide will be commissioned via NHS England Specialised Commissioning. Patients will be identified by Prof. Farooqi at University of Cambridge Metabolic Research Laboratories and treatment with setmelanotide will be initiated for eligible patients. Patients will then be referred to a regional centre for ongoing treatment and setmelanotide will be dispensed and delivered by the Homecare company used by the Trust. Rhythm will invoice the Homecare company for setmelanotide at the PAS

price. The Homecare company will subsequently invoice the NHS Trust and the Trust will invoice NHS England. (**Figure 1**).

Figure 1 Schematic overview of the Patient Access Scheme



3.10 Please provide details of the duration of the scheme.

There may be a change to the proposed patient access scheme following the introduction of other indications for setmelanotide. This is likely to involve an increase to the percentage discount if required to show cost-effectiveness in the new indication. Any increase in the percentage discount would be applied to all indications

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the evaluation? If so, how have these been addressed?

No issues have been identified.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4 Value for money

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the highly specialised technologies evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Highly Specialised Technologies Interim Evidence Submission Template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

N/A

4.2 If you are submitting the Patient Access Scheme at the end of the highly specialised technologies evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

N/A

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

The price of setmelanotide in the model has been adjusted to reflect the PAS price.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

Three interventional studies identified by the SLR investigated the efficacy and safety of setmelanotide for the treatment of obesity and/or hyperphagia caused by LEPR or POMC/PCSK1 genetic defects; information from these studies was used in the cost-effectiveness analysis.

An investigator-initiated, phase II study (RM-493-011) opportunistically enrolled two patients with POMC mutations and three patients with LEPR mutations across Germany, France and the UK. This study was primarily used to inform natural history of BMI-Z change in paediatric subjects (1, 2).

Two single-arm, phase III trials further investigated the efficacy and safety of setmelanotide in a larger series of patients with severe obesity caused by POMC (RM-493-012) and LEPR (RM-493-015) deficiencies (3). This study was used to inform baseline patient characteristics, patient response to setemelanotide, effectiveness of setmelanotide at one year (i.e. %change in BMI), and treatment-related adverse events. The values used in the model are described in Table 5 below.

Parameter	**Base-case values used in the model**
Mean age, POMC adult	25.4
Mean age, LEPR adult	26.3
% female, POMC adult	40.0%
% female, LEPR adult	60.0%
Mean age, POMC paediatric	12.8
Mean age, LEPR paediatric	12.4
% female, POMC paediatric	33.33%
% female, LEPR paediatric	60.00%

Baseline BMI distribution, POMC (20–25, 25–30, 30–35, 35–40, 40–45, 45–50, and ≥50)	[redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%
Baseline BMI distribution, LEPR (20–25, 25–30, 30–35, 35–40, 40–45, 45–50, and ≥50)	[redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%
BMI Z-score distribution, POMC (0.0–1.0, 1.0–2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and ≥4.0)	[redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%
BMI Z-score distribution, LEPR (0.0–1.0, 1.0–2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and ≥4.0)	[redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]%
Response rate, POMC adult	86%
Response rate, LEPR adult	60%
Response rate, POMC paediatric	86%
Response rate, LEPR paediatric	60%
BMI drop during trial, POMC adult	[redacted]
BMI drop during trial, LEPR adult	[redacted]
BMI drop during trial, POMC paediatric	[redacted]
BMI drop during trial, LEPR paediatric	[redacted]

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

It is not expected that there will be any additional costs associated with the implementation of the PAS. The Homecare provider will be invoiced for the discounted amount therefore no additional costs will be borne by the NHS.

Table 2 Costs associated with the implementation and operation of the Patient Access Scheme (PAS)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		
…		
Total implementation/ operation costs		

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

No additional treatment related costs are expected.

Summary results

Base-case analysis

4.7 Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 4).

Table 4 Base-case value for money results without Patient Access Scheme

	Intervention (Setmelanotide + BSC)	Comparator (BSC)
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	15.26
LYG difference	N/A	[redacted]
QALYs	[redacted]	3.94
QALY difference	N/A	[redacted]
QALYs (undiscounted)	[redacted]	[redacted]
QALY difference (undiscounted)	N/A	[redacted]
ICER (£)	£176,913	N/A

LYG: life-year gained; N/A: Not applicable; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.7 in appendix A.

Table 5 Base-case value for money results with Patient Access Scheme

	Intervention (Setmelanotide + BSC)	Comparator (BSC)
Intervention cost (£)	[redacted]	£1,769
Other costs (£)	[redacted]	£28,682
Total costs (£)	[redacted]	£30,451
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	15.26
LYG difference	N/A	[redacted]
QALYs	[redacted]	3.94
QALY difference	N/A	[redacted]
QALYs (undiscounted)	[redacted]	4.53
QALY difference (undiscounted)	N/A	[redacted]
ICER (£)	£141,550	N/A

LYG: life-year gained; N/A: Not applicable; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

[2] For outcome-based schemes, please see section 5.8 in appendix A

Table 6. Base-case incremental results with and without Patient Access Scheme

	Incremental results versus comparator (BSC)	
	Without PAS	**With PAS**
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
LY difference (undiscounted)	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
QALY difference (undiscounted)	[redacted]	[redacted]
ICER (£)	£176,913	£141,550

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

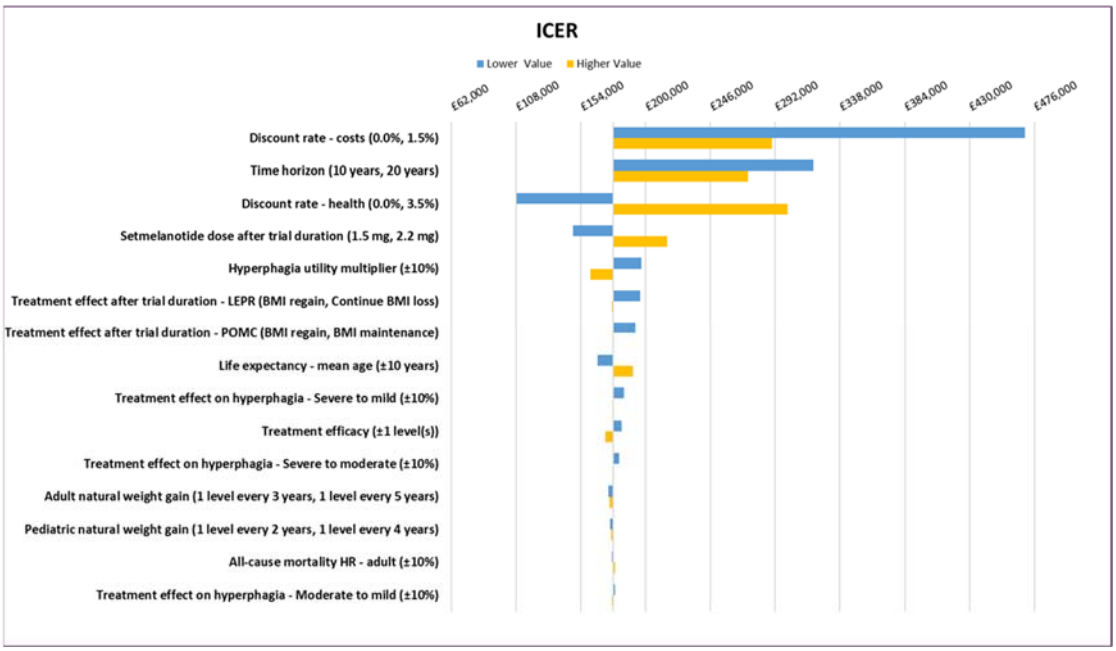
Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation. Consider using tornado diagrams.

The results of the deterministic sensitivity analysis are presented in

Figure 2below.

Figure 2. Tornado diagram of deterministic sensitivity analyses results



4.10 As shown in Figure 2, the primary drivers of model outcomes (defined as parameter values in which changes cause ICER to change by >25% of base case value) are the discount rate for costs, time horizon, and discount rate for health. Secondary drivers (defined as parameter values in which changes cause ICER to change by between 10% and 25% of the base case value) include the dose of setmelanotide after one-year (the trial duration), treatment effect after one-year, the hyperphagia utility, and the

mean life expectancy of patients. All other model parameter values impact the ICER by <10%.Please present scenario analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation.

Results of scenario analyses are presented in Table 8 below.

Table 8. Scenario analysis results

Scenarios	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£) Incremental (QALYs)
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Uniform baseline BMI distribution	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Distribution of POMC and LEPR based on trial population	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Distribution of paediatric and adults based on trial population	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: All responders have 1 level improvement in hyperphagia	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Inclusion of only comorbidities that are prevalent in paediatric subjects	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Incremental cost of BSC by BMI	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Response rate stratified by age	[redacted]	[redacted]	[redacted]	[redacted]

group based on trial				
Scenario 8: Hyperphagia mapping based on worst hunger score	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: Increased comorbidity disutility by 50%	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Account for acute cost of CV events	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: Utility scores decreased by 0.05 for BMI ≥ 50	[redacted]	[redacted]	[redacted]	[redacted]

4.11 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Results from the probabilistic sensitivity analyses are presented as scatter plots and cost-effectiveness acceptability curves in Figures 3 and 4 below respectively. The ICER and QALYs vary as expected as model inputs are varied. QALY gains were greater than [redacted] of PSA scenarios. The cost-effectiveness acceptability curve exhibited a steep and definitive switch to setmelanotide becoming more cost-effective than BSC at a WTP threshold of [redacted] per QALY gained.

Figure 3 Scatter plot of results from probabilistic sensitivity analyses

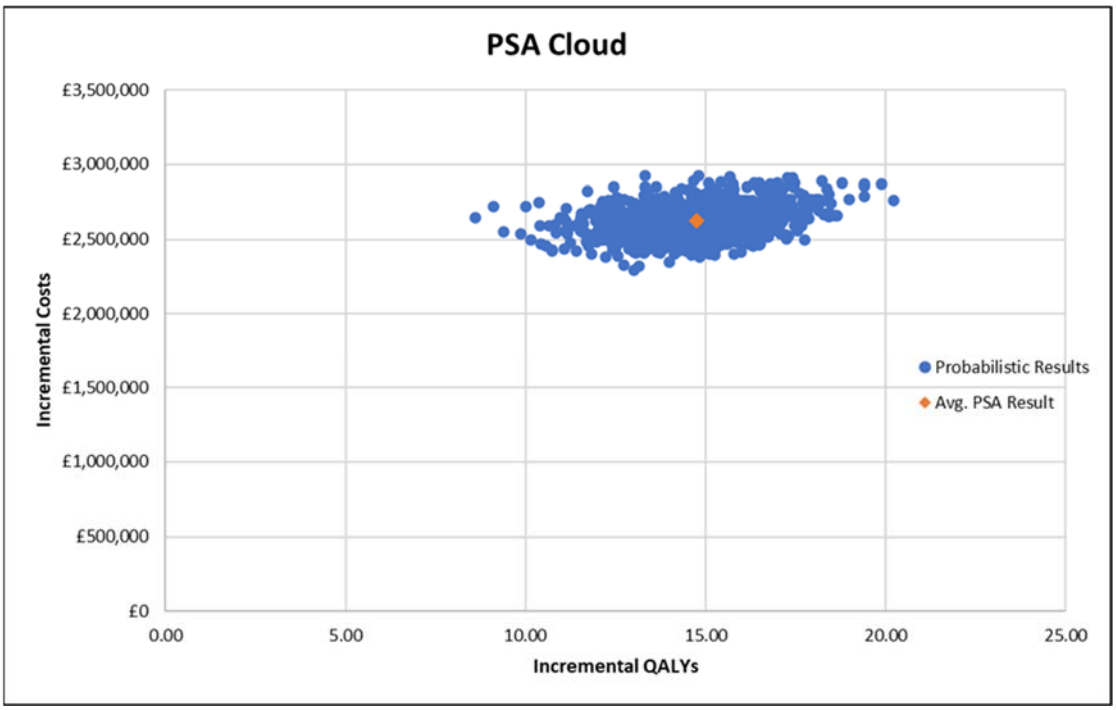
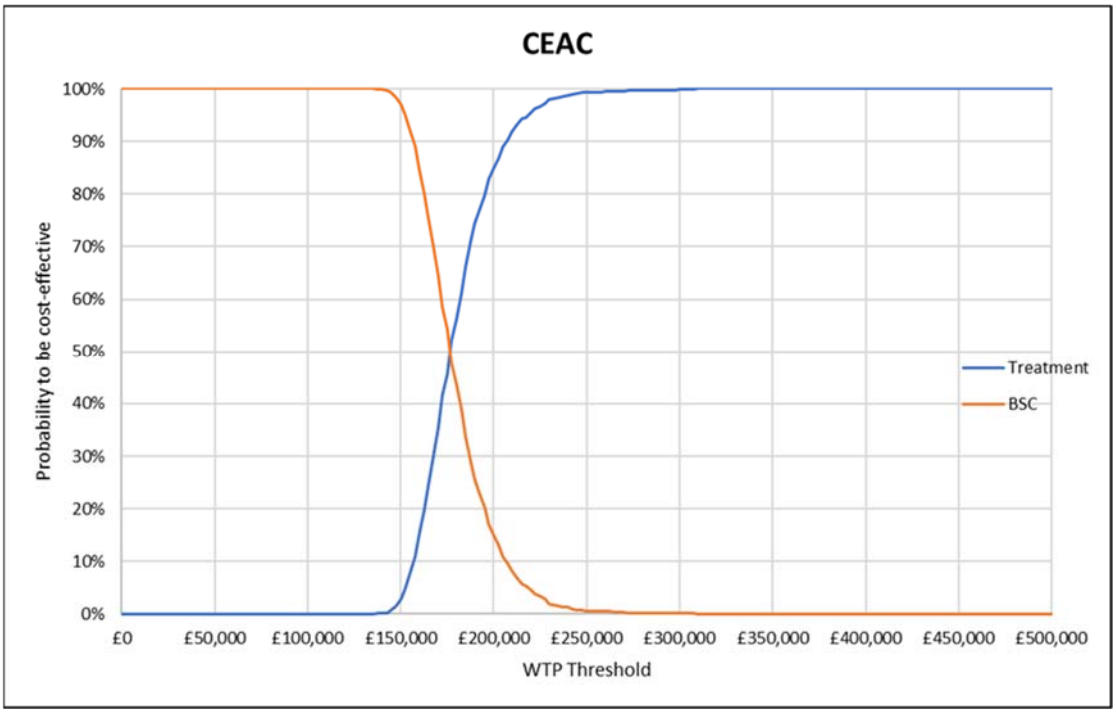


Figure 4 Cost-effectiveness acceptability curves based on results of probabilistic sensitivity analyses



4.12 If any of the criteria on which the Patient Access Scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

N/A

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results of the value for money analyses showing the impact of the Patient Access Scheme on the base-case and any scenario analyses. A suggested format is shown below (see table 4). If you are submitting the Patient Access Scheme at the end of the evaluation process, you

must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

Table 9 Results showing the impact of Patient Access Scheme on ICERs

	ICER for intervention versus:	
	BSC	
	Without PAS	With PAS
Base-case	**£176,913**	**£141,550**
Scenario 1: Uniform baseline BMI distribution	£173,856	£139,095
Scenario 2: Distribution of POMC and LEPR based on trial population	£180,010	£143,990
Scenario 3: Distribution of paediatric and adults based on trial population	£178,696	£143,018
Scenario 4: All responders have 1 level improvement in hyperphagia	£191,812	£153,471
Scenario 5: Inclusion of only comorbidities that are prevalent in paediatric subjects	£176,697	£141,369
Scenario 6: Incremental cost of BSC by BMI	£176,906	£141,362
Scenario 7: Response rate stratified by age group based on trial	£177,015	£141,631
Scenario 8: Hyperphagia mapping based on worst hunger score	£224,778	£179,686
Scenario 9: Increased comorbidity disutility by 50%	£177,134	£141,728
Scenario 10: Account for acute cost of CV events	£176,929	£141,567
Scenario 11: Utility scores decreased by 0.05 for BMI ≥ 50	£176,708	£141,386

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study

- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.4 Please specify the period between the time points when the additional evidence will be considered.

Response

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Response

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

Reference list

1. Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. N Engl J Med. 2016;375:240-6.
2. Clément K, Biebermann H, Farooqi IS, Van der Ploeg L, Wolters B, Poitou C, et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. Nature medicine. 2018;24(5):551-5.
3. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol. 2020;8(12):960-70.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

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

Clarification questions

July 2021

File name	Version	Contains confidential information	Date
[ID3764] Setmelanotide ERG clarification questions [redacted].docx	**1.0**	**Yes, redacted**	**11 August 2021**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Comparators

A1. Please provide further justification why some of the comparators presented in the NICE scope for this appraisal were excluded from consideration as inappropriate by the company, namely orlistat, methylcellulose and bariatric surgery. In particular, are there any published sources that the company can cite to support its decision to narrow the comparators from those listed in the NICE scope?

Orlistat, methylcellulose and bariatric surgery were excluded from the submission based on the feedback of Prof Farooqi and other international KOLs that these interventions are not effective for patients with POMC/PCSK1 or LEPR deficiency obesity and that they would not be used in clinical practice. The rationale being that none of these interventions target the underlying cause of obesity in these patients, namely hyperphagia, and that patients continue to experience unrelenting hunger despite the interventions. NICE has also previously ruled out orlistat as a relevant comparator in TA664 (liraglutide for managing overweight and obesity) and TA494 (naltrexone-buproprion for managing overweight and obesity) on the basis that experts

and consultees reported that standard management (diet and lifestyle interventions) is the only relevant comparator because orlistat is not often used in clinical practice.

We are not aware of any published evidence on treatment effect of methylcellulose or orlistat on weight loss or appetite regulation in patients with LEPR or POMC/PCSK1 deficiencies.

A publication by Poitou et al retrospectively analysed the outcome of bariatric surgery in eight patients with LEPR, POMC or MC4R variants. They found that all patients initially experienced weight loss but that this was followed by substantial weight regain and they concluded that the benefit/risk balance of performing bariatric surgery in these patients should be carefully evaluated by specialist centres before it is offered (1). The feedback we have received from UK KOLs is that it may be considered unethical to restrict the size of the stomach in a patient who has hyperphagia. Post-procedure weight loss following bariatric surgery is mainly dependent on mechanical restriction, and there is no additional effect on neurohormonal appetite regulation (2). Therefore, patients with LEPR or POMC/PCSK1 deficiency would not be expected to experience a decrease in appetite following bariatric surgery and consequently weight regain would be expected.

Generalisability

A2. The ERG understands from the clinical study reports that only one UK patient was included across the four submitted clinical trials (in RM-493-015). Please confirm if this understanding is correct. If so, what implications would you consider this limitation to have for the generalisability of the clinical evidence to a UK decision making context?

It is correct that study RM-493-015 included one patient from the UK. Additionally, study RM-493-011 also included one patient from the UK. Of the other patients in the studies, the vast majority were from other European countries, namely Germany, France, Spain, Belgium and the Netherlands, with the remainder coming from the US and Canada. In terms of ethnicity, [redacted] of patients in study 012 were Caucasian, [redacted] of patients in study 015 and [redacted] of patients in study 022. The Office of National

Statistics states that in 2011 in England and Wales, 80.5% of the population were considered White British with a further 4.4% identifying as Any Other White (3). It is therefore reasonable to assume that the data from the setmelanotide trials can be considered generalisable to the UK decision making context.

Dosing

A3. Priority question: The company's intended positioning of setmelanotide in a UK context is with a 2 mg initial dose for adult patients and a 1 mg initial dose for paediatric patients (company submission, Table 2). Please comment on any deviations from the proposed UK dosing regimen in the 4 clinical trials submitted, and what the impact may be upon correspondence of the evidence to the proposed UK licence and the generalisability of the evidence to a UK decision making context. For example, the ERG has noticed that the company reports a change in dosing in RM-493-015, where a 3 mg dose was used, on a recommendation from US regulators, however, authorities in France and Germany recommended the maximum dose to be 2.5 mg in amendments, with France later adjusting the dose back up to 3.0 mg.

The main difference between the doses given in the pivotal trials and the SMPC is that it was agreed by regulatory authorities that the titration period from the trials could be safely shortened to allow more rapid achievement of the therapeutic dose. The main impact on the generalisability of the data would be that patients in real-life practice may achieve their therapeutic dose more quickly than was seen in the trials; thus the trials can be seen as a conservative estimate of how quickly therapeutic effect may be achieved. The maximum dose of 3.0 mg was chosen for the SMPC as some patients in the pivotal trials required this dose to achieve their therapeutic response and no notable differences in safety/tolerability were observed at 3.0 mg compared with lower doses. The 3.0 mg dose is therefore in line with the proposed UK licence and no patients in the trials received a dose of setmelanotide that is higher than that which will be approved for use in the UK.

Adverse events (AEs)

A4. Priority question: The company states in its decision problem (Table 1) under outcomes that adverse events have not been considered in the model because "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". However, for example in RM 493-015 (Table 57), "treatment-emergent adverse events" are shown, totalling 15, of which 3 were serious, one of which led to a patient being withdrawn due to grade 1 eosinophilia that was deemed related to the study drug. Could the company please check that the information it reports on adverse events for each trial in the company submission is correct and confirm whether it would still consider it appropriate to exclude adverse events from consideration in the model?

The Company acknowledges that the following statement is incorrect: "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".

It would be correct to say that across the four clinical trials, no SAEs were reported that were considered related to study drug.

There was also one withdrawal from study 015 due to a non-serious, Grade 1 adverse event (eosinophilia) that was considered related to study drug. Grade 1 AEs are not routinely considered in economic evaluations unless they occur with very high frequency in the population as the cost and utility impact of such AEs is usually limited. Rather, economic models typically focus on the cost/utility consequences of severe AEs (grade 3 or 4). While the one AE did result in study withdrawal, in real world practice grade 1 AEs are not likely to be a reason for treatment discontinuation. Therefore, adverse events were not included in the model.

Population

A5. Priority question: The company has several population sets that are used in their analyses (e.g. Designated Use Set (DUS) and Full analysis set (FAS)) and has used different population sets for different endpoints in the analysis. For example, the primary endpoint in trial RM-493-015 has been measured on the FAS, where the key secondary endpoints have been measured on the DUS. Please explain the rationale behind using differing population sets for analysis.

The FAS was selected for the primary endpoint (proportion of patients who demonstrated at least 10% weight reduction at ~1 year) to give an overall estimate of setmelanotide's efficacy. It therefore makes sense to include all patients who were initiated on setmelanotide.

However, the trial protocol required patients to demonstrate ≥5 kg weight loss or 5% of body weight (if baseline weight was <100 kg) over the 12-week open-label treatment period in order to proceed into the double-blind, placebo-controlled withdrawal period and then continue on the study for the full 52 weeks. Patients who met these criteria were termed the Designated Use Set (DUS).

In clinical practice patients who do not meet these criteria would not continue on setmelanotide treatment, therefore, using the DUS for the secondary endpoints 'Mean percent change in body weight from baseline' and 'Mean percent change in weekly average daily hunger score' gives a more accurate reflection of setmelanotide's efficacy in the group of patients who will receive setmelanotide in clinical practice.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Please justify the deviation of model structure in this submission from that presented as Figure 11, p70 of Ara et al. 2012[1], a systematic review of clinical and cost effectiveness of using drugs in treating obese patients in primary care which informed the model structure in other appraisals [NICE technology appraisal (TA) 494 and TA664].

The model of Ara et al. was developed to evaluate the cost-effectiveness of treatments for general obesity and focused on the occurrence (and avoidance) of diabetes and cardiovascular events.

According to clinical experts who treat subjects with obesity arising from POMC/PCSK1 and LEPR-deficiency, hyperphagia and obesity in these patients arises due to defects in the MCR4 axis, and the most important complications of this defect are morbid obesity, and several key complications, 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.

While T2DM and CV disease were also noted to be potentially important in the long term for POMC/PCSK1 and LEPR-deficiency and are therefore included in our model, the limited available data from the pivotal trials of setmelanotide suggest that few subjects have these complications when starting treatment due to young age. Furthermore, relatively early mortality in POMC/PCSK1 and LEPR-deficient subjects could prevent the manifestation of CV events. Therefore, we felt that the structure of Ara et al. included excessive granularity in the representation of T2DM and CV disease and insufficient detail surrounding the other elements described above for the purposes of an economic evaluation.

[1] Ara R, Blake L, Gray L, et al. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review. Health Technol Assess. 2012;16(5):iii-xiv, 1-195. doi: 10.3310/hta16050.

B2. Please elaborate on any reasons, other than to have a smaller number of health states, for assuming hyperphagia independent of patients' BMI-based health states in the model. Further, please indicate how the structural uncertainty arising from this simplifying assumption has been accounted for in the model.

It should be noted that the model structure does capture hyperphagia status and its changes over time (mild, moderate, or severe) within each BMI class health state rather than via independent health states stratified by both BMI and hyperphagia. There were three main reasons for this decision.

1. While initial conceptualization of the model structure did consider including separate health states by hyperphagia status for each BMI class, due to evidence gaps, transition probabilities between such health states would be unable to be estimated. Hence, the majority of hyperphagia health states were expected to degenerate into the BMI class states currently represented. Our systematic literature review did not, in fact, find any published evidence to inform the more complex structure. A formal structural sensitivity analysis was therefore not possible.

2. According to clinical expert opinion, the phenotype of patients will change following response to setmelanotide due to reductions in hyperphagia driven by direct targeting of the mechanistic defect in the MCR4 axis in these patients. The experts suggested that this effect will be largely independent of the patients' BMI class.

3. Given the large number of evidence gaps for the patient populations of interest, an approach was chosen to keep the model structure as simple as possible while still capturing the essential components key to the economic evaluation by avoiding a "health state explosion", as noted in the question.

In the absence of the data necessary to implement and test a formal structural sensitivity analysis, we performed a scenario analysis in which the baseline hyperphagia status was varied to evaluate the impact of this baseline variation on results, as described in the submission.

Model framework

B3. Please explain why LEPR inputs appear in the 'Parameter' sheet when 'All population' is selected in the model? It is disorienting to see LEPR inputs throughout when 'All population' has been selected. Also, please explain why the 'Run Model' macro was needed to run the deterministic analysis.

A 'Run Model' macro is needed as LEPR and POMC/PCSK1 subpopulations are run sequentially in the model and the results from each run is saved in the 'Results Report' tab. The weighted average results across the two subpopulations are then computed and reported in the 'Results' tab. The 'Parameter' sheet shows the inputs from the last subpopulation which was run by the 'Run Model' macro (i.e., LEPR inputs in the base case settings).

Dosing

B4. The model appears to base the cost of setmelanotide in Year 1 on the average dose given to POMC and LEPR adult and paediatric patients in trials NCT02896192 and NCT03287960. Please provide the average setmelanotide dose separately for paediatric patients and adults in each trial.

The overall mean dose observed in all patients in the trials (NCT02896192 and NCT03287960) was considered as the average dose during the trial period. The overall mean dose for patients responding to setmelanotide observed at 52 weeks was considered as the dose post trial period in the base case analysis due to the small number of patients in each subpopulation and the higher uncertainty around dose estimates for each separate subpopulation.

The 'Settings' tab has been modified to enable consideration of the average setmelanotide dose for paediatric and adult patients based on the analysis of dosing data for all patients in each trial (see table below). 'Costs' sheet (rows 21:23) and 'Parameters' sheet (rows 109:112) are updated to accommodate this new scenario accordingly.

Population	POMC/PCSK1	LEPR
Paediatric Dose	[redacted] mg	[redacted] mg
Adult Dose	[redacted] mg	[redacted] mg

The ICER increased under this scenario to £198,916/QALY.

Discounting

B5. Priority question: Please justify the usage of 1.5% discount rate for health, given the evidence to support the long-term treatment benefit is limited and the patients are not restored to full or near full health, although increased life expectancy was noted. For more information about discounting in HST, please refer to section 47 of the HST interim process and methods guide.

NICE accepts a non-reference case discount rate of 1.5% for costs and health effects when the 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 at least 30 years). Clinical experts have indicated that with sustained setmelanotide treatment, patients with POMC/PCSK1 and LEPR-deficiency will move to disease trajectories that more resemble those of patients with stabilized BMIs indicative of overweight (25-30) or obese class I (30-35), both of which are closer to full health. Furthermore, as seen in the results of the base-case, setmelanotide extends the average life expectancy of patients by close to [redacted] years ([redacted]years for POMC/PCSK1 patients and [redacted] years for LEPR-deficient patients). In addition, the benefits of setmelanotide treatment arise in part due to the significant reduction in severe hyperphagia; this provides profound QoL improvements that are realised for the patients' full and extended life span. We believe that a 3.5% discount rate would substantially undervalue the sustained benefits of setmelanotide in later years of life.

Furthermore, a differential discount rate has been previously used and accepted by NICE (mifamurtide submission, TA235).(National Institute for Health and Care Excellence 2011) The cost-effectiveness estimates in that appraisal were sensitive to the discount rate used; the committee was provided with a clarification note for considering using the discount rates of 3.5% for costs and 1.5% for health effects the

in sensitivity analyses, as the treatment effects were both substantial and sustained over a very long period.

Treatment effect/Response

B6. Priority question: In the base case analysis two different approaches were used to estimate the treatment effect (after the trial duration), for patients with POMC and LEPR deficiency i.e. patients with POMC deficiency were assumed to experience continued BMI reduction, while patients with LEPR deficiency were assumed to have stable BMI. Please clarify:

a) **the rationale as to why different assumptions were made by subtype;**

This assumption was made based on input from clinical experts regarding the differences between the nature of obesity arising from POMC/PCSK1-deficiency and LEPR-deficiency, as well as how patients with POMC/PCSK1 and LEPR deficiency may differentially respond to treatment with setmelanotide over the long-term. According to the clinical experts, hyperphagia and obesity in LEPR-deficient patients is usually more severe than seen in POMC/PCSK1 deficiency as it is mediated by both melanocortin-dependent (setmelanotide-responsive) and melanocortin-independent (setmelanotide-unresponsive) pathways, while the melanocortin-dependent (setmelanotide-responsive) pathway predominates in patients with POMC/PCSK1 deficiency. While obesity in POMC/PCSK1 deficient patients is still severe compared to the general obesity population, and the predominance of the setmelanotide-responsive pathway in these patients and available subject-level data suggested these patients are more likely to experience [redacted]. As a consequence, a [redacted] treatment was implemented in the model for LEPR-deficient subjects as a conservative assumption.

b) **how extrapolation of effect relates to the assumption of long-term plateaus in weight loss, as inconsistent information is provided across Tables 66 and 80; and**

The assumed base case treatment efficacy after the trial period for the two subtypes are:

- LEPR patients will [redacted] the BMI class observed at the end of trial period.

- POMC/PCSK1 patients will [redacted] experiencing BMI [redacted] until they reach BMI of [redacted] for adults and BMI Z-score of [redacted] for paediatric patients, after which they will maintain that BMI class. This implementation was based on the opinion of clinical experts.

Tables 66 and 80 used different language to explain this logic but the description of the logic between the two tables is consistent.

c) why, given the stated assumption of long-term plateau, health states of BMI 20-25 are included in the economic model.

The trial data indicated that some patients with POMC/PCSK1 deficiency moved into normal BMI class (20-25) during the first year of treatment, so BMI class 20-25 (normal weight) was incorporated into the model. The model implementation is therefore consistent with the trial data up to 52 weeks.

Clinical experts also suggested that patients with POMC/PCSK1 deficiency are expected to stabilize at BMI class of [redacted] with sustained setmelanotide treatment. The model base case includes a more conservative lower limit of BMI (30-35). Scenarios in which patients move into BMI class 20-25 or 25-30 in the long term could be assessed using the current model structure.

B7. Priority question: Given that the model structure is based on BMI class, please explain why post-trial efficacy and treatment response based on BMI class was not considered in the base case?

The model provides two options to define efficacy and response rate: overall population response and by BMI class. Due to limited data characterizing post-treatment response (i.e., small number of patients and in some cases lack of patients in certain BMI classes at baseline) and the consequent potential uncertainty around computed efficacy/response by BMI class, the approach using post-trial efficacy defined by overall population response was deemed more appropriate for the base case.

A scenario analysis is included in the submission document in which the post-trial efficacy is defined by BMI class, but the result may be difficult to interpret due to the

aforementioned small patient numbers and associated uncertainty in transition probability estimates between some BMI classes.

B8. Priority question: The ERG noted that the effect of treatment on hyperphagia after the trial period (one year) was assumed to be maintained through patients' lifetime based on expert opinion. However, please provide any relevant data or literature to support this claim.

The SLR did not find any evidence of published evidence related to the long-term effect of setmelanotide on hyperphagia. Consequently, the assumption of the maintenance of setmelanotide's effect on hyperphagia was made based on discussions with clinical experts, who indicated that the phenotype of patients treated with setmelanotide is expected to change more towards disease trajectories that more resemble those of patients with stabilized BMIs indicative of overweight (25-30) or obese class I (30-35) due to the drug's direct effect on the defective MCR4 axis and concomitant expected reductions in hyperphagia, so long as treatment is maintained.

B9. For patients with POMC deficiency (treated with setmelanotide), it is assumed that BMI reduction would continue after the trial i.e. drop one BMI class every 2 years and stabilise at specified BMI/BMI-Z scores. It would be helpful if you could outline the rationale underpinning these assumptions.

Clinical experts suggested that patients with POMC/PSCK1 deficiency are expected to [redacted] BMI after trial duration, [redacted] as observed during the trial. We therefore assumed [redacted] of reduction in BMI class every [redacted] years in the base case. Two scenarios exploring this uncertainty were added into the DSA: varying the BMI reduction in POMC/PCSK1 patients by & [redacted] every [redacted] and [redacted] every [redacted] years after trial duration (DSA row 45). As shown in the scenarios and the tornado diagram for the DSA, the model is not sensitive to this parameter.

B10. Table 22 of the submission indicated that there was 11.1% discontinuation from the treatment for patients with POMC/PCSK1 deficiency. However, treatment discontinuation has not been included in the model. Please clarify.

Treatment discontinuation is not included in the model as there were no major treatment discontinuation events related to the administration of setmelanotide in the

index trials or the extension study for POMC/PSCK1 and LEPR patients. The discontinuations observed were due to other causes either deemed not relevant to real world practice or captured in the model based on response assessment at 3 months.

- Two patients discontinued Study RM-493-015; 1 patient died due to injuries sustained as a passenger in a car accident and 1 patient discontinued due to mild (grade 1) eosinophilia, which is typically grounds for continued monitoring of subjects in the real world, but not discontinuation.

- [redacted] patients discontinued Study RM-493-012; [redacted] for lack of efficacy (captured in 3-month response assessment in the model), [redacted] following a protocol violation (patient [redacted]), and [redacted] was lost to follow up for unknown reasons.

- The 11.1% discontinuation in the RM-493-022 trial reported in Table 22 of the submission is based on the withdrawal of [redacted] from the extension study before completing 37 weeks of treatment which was determined to be due to adverse events not related to the study drug.

B11. Please explain the rationale behind applying hyperphagia related treatment effect at the start of the first cycle in the model, while the treatment response has been measured only after 12 weeks.

The hyperphagia effect is observed very rapidly within the first 2-3 weeks of therapy as seen in the results from index trials. In the CEM, annual cycles are considered in the Markov structure and a simplifying assumption that the impact on hyperphagia severity is effective immediately (i.e., at the start of first cycle) was made.

To address ERG comments, a new scenario option was added into the 'Settings' tab to delay the onset of impact on hyperphagia severity till start of year 1 (i.e., at the end of first cycle). This implementation had minimal impact on the model outcomes (the ICER slightly increased under this scenario from £176,913/QALY to £178,488/QALY).

Mortality

B12. Priority question: Please clarify why different approaches were used to parameterise mortality for non-responders and responders, and if possible, re-express life expectancy estimates in equivalent state-specific hazard ratios (HRs).

We assumed that the mortality for non-responders to setmelanotide is similar to patients on BSC and based on clinical expert opinion; patients with LEPR and POMC/PCSK1 deficiencies have much worse survival than general obesity population if untreated. Responders to setmelanotide were assumed to follow a disease trajectory that is similar to general obesity patients and hence the life expectancy of responders was modelled based on a set of hazard ratios (HRs) stratified by BMI class from general obesity literature which were then applied to background mortality for the general population derived from the UK life tables. Clinical experts also indicated that non-responders to setmelanotide and LEPR and POMC/PSCK1 patients on BSC would be expected to die at younger ages. Adjusting the HRs provided for general obesity to achieve such survival outcomes would not be appropriate as the base risk of mortality in patients of younger ages is relatively low. Hence, the mortality for non-responders was modelled based on parametric fits to mean life expectancy distributions based on clinician's estimates of mean and maximum life expectancy.

To address ERG comments, an option for modelling mortality for non-responders to setmelanotide and patients with BSC based on state-specific hazard ratios has been added in the 'Settings' tab. The structure has been updated accordingly in the <Engine> sheets and <Mortality for NR (ERG Comment)> sheet. A new parameter "mortality HR multipliers" was also introduced to adjust the HRs derived from general obesity literature for non-responders. The multipliers were then calibrated to match the mean life expectancy for non-responders to inputs provided by KOL for POMC/PSCK1 and LEPR population. The calibrated mortality HR multipliers required to match the mean life expectancy estimates of 45 and 30 years for POMC/PSCK1 and LEPR patients are [redacted] for POMC/PSCK1 and [redacted] for LEPR, respectively. These HRs are approximately [redacted] times greater than those reported for BMI-dependent mortality.

B13. Priority question: Please provide an option in the model to test the HRs stratified by BMI level from general obesity literature for non-responders to setmelanotide and patients on best supportive care.

As mentioned in response to B12, to address ERG comments, an option for modelling mortality for non-responders to setmelanotide and patients with BSC based on state-specific hazard ratios has been added in the 'Settings' tab. Under this scenario, the life expectancy of patients on setmelanotide is only driven by change in BMI and hence much closer to patients on BSC (incremental LYs decreases to [redacted] years from [redacted] years). The incremental QALYs decreases to [redacted] years from [redacted] years and ICER increases to £231,290/QALY from £176,913/QALY. The gain in QALYs in this implementation is mainly derived by the improvement of the QoL of patients accrued over their extended lifetime due to decrease in hyperphagia severity.

Utilities

B14. It would be helpful if you could provide further detail surrounding the approach to linearly extrapolating utility values for the paediatric population in the model.

This was a simplifying assumption due to lack of data. In response to the ERG comments, an option for non-linear extrapolation of utilities for the paediatric population has been added in the 'Settings' tab. The updated approach takes the ratio of reported utilities for adults at two adjacent BMI categories and then applies that ratio to the available paediatric utilities from the literature. BMI mapping is also considered here. The impact of selecting non-linear extrapolation on model outcomes was minimal (the ICER slightly increased under this scenario from £176,913/QALY to £176,739/QALY).

Sensitivity analysis

B15. Priority question: Table 86 of the company submission and the one-way sensitivity analysis in the model have mentioned that the discount rate for costs were varied between 0%-1.5%, while the base case value is 3.5%. Please clarify.

In the DSA, the impact of changing the base case cost discount rate of 3.5% to 0% and 1.5% was explored. We clarified this language in the submission document. New scenarios for cost discount rate at 3% and 5% have been added to the DSA (DSA sheet - row 19).

Model validation

B16. Please elaborate on any attempt to validate the base case model results (incremental life year gain and average life expectancy) via clinical opinion or by other means.

We have not yet validated the base case model results via clinical opinion but validated the key survival outcomes of the model against inputs provided by clinical experts. This information was used to inform the survival inputs and assumptions in the model (i.e., average life expectancy: [redacted] years for POMC/PCSK1 and [redacted] years for LEPR patients). Base case average life expectancy values reported for BSC from the model are closely aligned with the clinical expert inputs (i.e., [redacted] years for POMC/PCSK1 and [redacted] years for LEPR patients).

Section C: Textual clarification and additional points

C1. Priority question: The ERG assumes that probabilities used for transition among the different hyperphagia severity states post-treatment were derived from change in hunger scores. Please confirm whether this is the case. Additionally, were these changes in hunger scores obtained from the clinical study reports or trial publications, and did they include data from the total cohorts or pivotal cohorts only?

The Company confirms that the transition probabilities across different hyperphagia severity states post-treatment were derived from change in patients' hunger scores from baseline. However, when assigning patients to one of the three severity classes of hyperphagia (mild, moderate or severe), clinical investigators looked at hyperphagia in its holistic definition. That is why, there is no linear correlation between hunger score and hyperphagia. A patient with moderate hunger could be classified as severely hyperphagic. Investigators in setmelanotide's clinical studies have confirmed that [redacted]

patients had [redacted] hyperphagia at baseline. The Company has conducted exit interviews with patients from the trials based on which they were able to [redacted] of patients' hyperphagia severity at the end of these trials.
The Company would like to emphasise on the holistic definition of hyperphagia, which is broader than hunger. Hyperphagia is described as an overwhelming, heightened, and relentless hunger mimicking feelings of starvation; longer time to reach satiety and shorter duration of satiety; severe preoccupation with food; persistent and potentially extreme food-seeking behaviours (such as night eating, stealing food, and eating non-food items); and distress or inappropriate behavioural response if denied food (4). Food intake was not controlled in clinical trials so it would be fair to say that measuring hyperphagia solely by hunger score is an underestimation of hyperphagia's effect as it also depends on number of meals taken per day.

C2. Section 2.2.6 is referenced twice in the cost effectiveness section (12.2.1.3) when discussing treatment effect. However, section 2.2.6 does not appear to exist in the report. Is this an error? Please clarify which pages specifically provide information on natural weight gain trajectories and the treatment effect on hyperphagia.

There appears to be a minor error with the cross-reference of the abovementioned section. Section 2.2.6 is supposed to refer to section 12.2.6 "Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission". Table 80 (p.190 and 191) within section 12.2.6 states the natural weight gain assumed in the model i.e. X BMI health states every Y years, as well as treatment effect on hyperphagia.

C3. Table numbers 6 to 18 in the text do not refer to the correct table headings. Please confirm whether Table 6 in the text is intended to refer to Table 5, Table 7 in the text to Table 6, and so forth, up to Table 18 in the text; as the hyperlinks suggest? If this is the case, please correct the misalignment.

Yes, there is an issue with the numbering and cross-referencing of Tables 6 to 18 in the submission. We confirm that Table 6 is intended to refer to Table 5 in the text,

Table 7 refers to Table 6 etc. This minor error will be fixed in the updated ACIC version of setmelanotide submission document.

Reference List

1. Poitou C, Puder L, Dubern B, Krabusch P, Genser L, Wiegand S, et al. Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes. Surgery for Obesity and Related Diseases. 2021.

2. Aslan IR, Ranadive SA, Valle I, Kollipara S, Noble JA, Vaisse C. The melanocortin system and insulin resistance in humans: insights from a patient with complete POMC deficiency and type 1 diabetes mellitus. International journal of obesity. 2014;38(1):148-51.

3. Statistics OoN. Ethnicity and National Identity in England and Wales: 2011 2012 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11.

4. Heymsfield SB, Avena NM, Baier L, Brantley P, Bray GA, Burnett LC, et al. Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia. Obesity. 2014;22(S1):S1-S17.

1. **In response to question B12 in the clarification document, the following was stated: 'The calibrated mortality HR multipliers required to match the mean life expectancy estimates of [redacted] and [redacted] years for POMC/PSCK1 and LEPR patients are [redacted] for POMC/PSCK1 and [redacted] for LEPR, respectively'.**

   It is not clear how the life expectancy estimates were converted to the equivalent HR multiplier. Please clarify how this was done?

   Please also confirm whether these data are CiC or AiC.

   In the original model engine, the structure of mortality for responders was BMI specific, and the risk of mortality by BMI class was computed based on HRs (derived from Bhaskaran et al. [1]) applied to general population mortality (i.e., life tables). To address B12/B13, we took two actions:

   - Modified the mortality logic for non-responders and patients on BSC to align with the structure for responders.
   - Introduced "mortality HR multiplier" as a new parameter in the model to explore the impact of increasing the hazard of death for non-responders/patients on BSC.
     - This multiplier is applied to all mortality HRs by BMI class once the option for scenario B12/B13 is selected in the Settings tab.
     - The default value for this multiplier is 1 (i.e., no difference). To address the request in B12, we calibrated the value of this multiplier by trial and error, running the model multiple times until we achieved a mean life expectancy in the model that was similar to the mean life expectancy estimates provided by clinical experts.
     - The calibrated multipliers (14.97 for POMC/PSCK1 and 80.18 for LEPR) should be applied to the baseline BMI specific HRs in the model to get the equivalent state-specific HRs requested in B12.
   - Life expectancy data are based on KOL input and are considered AiC. HR multipliers are part of the HEOR modelling and are considered CiC

[1] Bhaskaran K, et al. "Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults inthe UK". Lancet Diabetes Endocrinol (2018); 6: 944–53

2. **In response to question C1 in the clarification, it was indicated that a holistic definition of hyperphagia, broader than hunger, has been used. However, it is still not clear how the proportions below were derived:**

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

Please clarify the method by which these proportions were derived, using this holistic definition?

As detailed in the evidence submission, hyperphagia is characterised by:

- "Overeating": eating beyond the energy intake required for body size and body composition
- "Hunger" and increased time / amount of food required to reach satiation
- "Hyperphagic drive": preoccupation with food or food seeking behaviors
- Distress and functional impairment when denied food

In contrast to more common food-seeking behaviors, such as binge eating, hyperphagia is distinctly characterized by pathological and insatiable hunger associated with persistent and potentially extreme or severe food seeking behavior, such as stealing food, waking at night to find food, eating food others leave behind, or eating non-food items.[2,3]

Results from a qualitative study conducted in patients with LEPR or POMC deficiency corroborated the degree of hyperphagia severity experienced by these patients[4].

- One patient stated [redacted]
- Another patient noted [redacted]
- One patient with POMC deficiency shared [redacted]

[2] Heymsfield, Steven B., et al. "Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia." Obesity 22.S1 (2014): S1-S17.
[3] Dykens, E. M., Leckman, J. F., & Cassidy, S. B. (1996). Obsessions and compulsions in Prader-Willi syndrome. Journal of Child Psychology and Psychiatry, 37(8), 995-1002.
[4] Qualitative Interviews with Setmelanotide Trial Participants, Rhythm Pharmaceuticals, Data on File 2021.

Collectively, these patient perspectives bolster the view point that hyperphagia creates a significantly high burden for patients beyond the common definitions and concepts of hunger and overeating.

There is not validated tool to measure hyperphagia in POMC or LEPR deficiency. Upon discussions with regulatory authorities, Rhythm included evaluations of changes in hunger as key secondary endpoints in the open-label phase 3 studies of setmelanotide (RM-493-012 and RM-493-015). Consequently, the MHRA label was granted stating "*IMCIVREE is indicated for the treatment of obesity and the control of hunger."*

While the measure was adequate to address needs of the regulatory agencies, the degree of severity associated with hunger that are more reflective of the hyperphagia experienced in these patients may have been underrepresented by this measure. In addition, hunger is dependent on food intake and meal frequency, and those were not controlled (normalized) in trials RM-493-012 and RM-493-015. This introduces another variable that may skew the relative impact of setmelanotide on hunger and hyperphagia *(please see subsequent sections on patient interviews)*. To illustrate the situation:

- A patient taking 7 or 8 meals per day and eating once or twice per night, would be characterized as having severe hyperphagia: large overeating, strong hyperphagic drive,…
    - But at any point in time, this patient may only have moderate hunger, due to the high frequency of food intake
- Following treatment with IMCIVREE that patient may limit the number of meals per 24 hours to 3 or 4, having significantly reduced overeating and hyperphagic drive
    - This results in the weight and BMI reduction seen in the trials
    - However, hunger at any point in time including the morning may remain moderate as the interval between meals increases significantly

To measure QALY generation through IMCIVREE, we believed inclusion of hyperphagia severity health states represented the disease more accurately than the measure of hunger.

The baseline hyperphagia severity distribution in patients (mild, moderate or severe) was derived from the opinion of a UK clinical expert, who noted that the majority of POMC/PCSK1-deficient and LEPR-deficient patients exhibit moderate to severe hyperphagia, with the condition tending towards greater severity in LEPR subjects.

Table 1: Baseline distribution of hyperphagia in POMC and LEPR patients:

	POMC/PCSK1	LEPR
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Total	[redacted]	[redacted]

Upon therapy with IMCIVREE, the effect of treatment on hyperphagia is confirmed by both clinical experts and patients. For the model, we used reduction in hunger scores as a basis for hyperphagia transition probabilities but also included input from clinical experts and from patients in order to fully represent the effect of therapy on hyperphagia

NOTE: These hyperphagia transitions probabilities only apply to the patients responding to IMCIVREE ("Responder Population in the model"), as Loss of weight and reduction in BMI is a phenotypical response to reductions in hyperphagia

Reduction in hunger score

In study RM-493-012, 50% of patients showed a reduction of > 25% in highest hunger score. In study RM-493-015, 72% of patients showed a reduction of > 25% in highest hunger score

To assess the effect of therapy on hyperphagia, a hunger score of >=7 (on a scale of 0-10) was considered to correspond to severe hyperphagia, a hunger score of 4-6 was considered to correspond to moderate hyperphagia, and a score of <=4 was considered to correspond to mild hyperphagia based on discussion with clinicians who were consulted in the design of the vignette study who had experience treating patients with hyperphagia.[5]

Using these definitions, the changes in hyperphagia severity are depicted below for POMC and for LEPR responders to therapy for both worst hunger and average hunger scores (when data available and reported by patients – studies RM-493-012 and RM-493-015)

Table 2: Hyperphagia Severity Levels based on Hunger Scores in Responders

POMC/ PCSK1 Patients	**Worst Hunger**		**Average Hunger**	
	Baseline	Responders at 52 Weeks	Baseline	Responders at 52 Weeks
Patient 1	[redacted]			
Patient 2				
Patient 3				
Patient 4				
Patient 5				
Patient 6				
Patient 7				
Patient 8				

LEPR Patients	**Worst Hunger**		**Average Hunger**	
	Baseline	Responders at 52 Weeks	Baseline	Responders at 52 Weeks
Patient 1	[redacted]			

[5] Howell T., Matza L., et al. Health State Utilities Associated with Hyperphagia. Accepted as poster presentation at Virtual ISPOR Europe, Nov 30-Dec 3 2021.

Patient 2	[redacted]
Patient 3	
Patient 4	
Patient 5	

Input from clinical experts

Clinical experts confirm that IMCIVREE has a significant impact on hyperphagia that goes beyond the impact on hunger measured in the trial:

[redacted]

Input from patients in exit interviews

Interviews were conducted with POMC or LEPR deficiency patients participating in an on ongoing clinical trial of setmelanotide (RM-493-022) [6]. Patients were asked to describe their experiences with hyperphagia after IMCIVREE treatment. While hunger is still present, patients described large reductions in hyperphagia-related symptoms.

- One patient with LEPR deficiency stated [redacted]
- Another patient with POMC deficiency explained [redacted]

The combination of input described above: changes in hunger score, physician input and patient input was used to develop the transition stage probabilities used in the model for responders to therapy (see table below):

Table 3: Hyperphagia transition state probabilities used in the model

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

These transition stages lead to a distribution of hyperphagia in responders, that we believe is a conservative representation of clinical effect and is line with both clinicians' and patients' input. As we could not differentiate between POMC and LEPR based on available information we used a similar distribution for the two populations.

[6] Qualitative Interviews with Setmelanotide Trial Participants, Rhythm Pharmaceuticals, Data on File 2021.

Table 4: Hyperphagia severity at baseline compared to hyperphagia severity at 52 weeks in Responders (using transition probabilities used in the model)

	POMC/PCSK1			LEPR	
	Baseline	52 Weeks		Baseline	52 Weeks
Mild	[redacted]	[redacted]		[redacted]	[redacted]
Moderate	[redacted]	[redacted]		[redacted]	[redacted]
Severe	[redacted]	[redacted]		[redacted]	[redacted]
Total	[redacted]	[redacted]		[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS ENGLAND & IMPROVEMENT**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHS England clinical commissioning policies for this indication.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Although there is no specific highly specialised (HSS) for this condition there is one centre of excellence and expertise in England. NHS England will work closely with the service to ensure they are able to prescribe the drug, provide advice to referrers and monitoring patient outcomes. Due to the rarity of the condition the clinical pathway from local centres is not well defined.
8. What impact would the technology have on the current pathway of care?	There is no effective pharmacological therapy in place for either condition so the this would have a significant impact on the current pathway.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This drug is not routinely commissioned by NHSE so is not in use in the local health economy.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology, if approved, would provide the first pharmacological treatment option for patients with this condition.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is anticipated the technology would be administered through the national centre
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Genetic testing is required to confirm the diagnosis.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No additional equality issues
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Mars Skae**
2. Name of organisation	**Royal Manchester Children's Hospital (on behalf of the BSPED)**

3. Job title or position	**Consultant Paediatric Endocrinologist**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.) **I am submitting my appraisal on behalf of the British Society of Paediatric Endocrinology and Diabetes (BSPED).**
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Proopiomelanocortin (POMC) is the precursor for melanocyte-stimulating hormone (MSH). It plays a pivotal role in the regulation of satiety and energy expenditure. In the hypothalamic leptin–melanocortin signalling pathway, melanocyte-stimulating hormone transmits the anorexic effect of leptin through the melanocortin-4 receptor (MC4R). Setmelanotide, an eight-amino-acid cyclic peptide also known as RM-493, is a melanocortin-4 receptor agonist. It potentially offers a mechanism-based treatment of the obesity in proopiomelanocortin deficiency, in effect providing a substitute for the absent melanocyte-stimulating hormone that could bind and activate the melanocortin-4 receptor. The main aim of this treatment if therefore to: 1. Assist patients with patients with genetic forms of obesity due to POMV and LEPR mutations to achieve weight loss. 2. Reduce the life impacting symptom of hyperphagia which occur in this condition. 3. Reduce the risk of metabolic comorbidities associated with obesity in these conditions.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In short-term phase 1b studies of Setmelanotide, an average weight loss of approximately 1 kg per week has been observed for up to 4 weeks. In a phase 3 multicentre trial of Setmelanotide in 10 patients with POMC deficiency, 80% of patients achieved >10% weight loss from baseline to 1 year of treatment with significant reduction in fasting glucose and triglyceride levels.(Clement K et al, Obesity Week 2019). A similar trial in LEPR deficiency demonstrated a weight loss >10% in 45% of cases with 73% of participants having ≥25% reduction in “most hunger” scores from baseline to ~1 year on therapeutic dose. Only significant reductions in LDL-cholesterol were noted in this cohort (Van de Akker E, Obesity Week 2019). Further supplemental studies found that the mean reduction in baseline body weight for the supplemental POMC deficiency obesity patients was -26.3 %, and the mean reduction in body weight for the supplemental LEPR deficiency obesity patients was -13.2 %. The estimated mean percentage reduction in most hunger score for evaluable patients in the supplemental cohorts was -57.3 % in adults. (Rhythm Pharmaceuticals, Globe Newswire Jul2020).

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. We have limited effective treatments for improving BMI SDS and hyperphagia in POMC deficiency in particular.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	This condition is currently treated with dietary restriction and increased exercise to ensure weight maintenance, however in most cases this is not effective and efficacy of lifestyle management is limited. Routine screening for complications of excess weight is carried out.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The majority of guidelines for the treatment are based on research study protocol guidelines at this present time because this is not a standard therapy that is used in clinical care.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Clinicians would be directed by the pharmaceutical company manufacturing the drug and protocols from external users abroad and research trials when using this medication.

• What impact would the technology have on the current pathway of care?	The technology would be the only treatment available for managing certain genetic conditions causing early onset obesity and hyperphagia. This would make weight management of these patients more effective, thus preventing more complications of obesity.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Setmelanotide is not currently used in standard clinical care for genetic conditions causing early onset obesity and hyperphagia. There are no currently available treatments for tackling hyperphagia in the UK. Previous use of Sibutramine was withdrawn due to significant risk of side-effects by NICE. Therefore the use of Setmelanotide will be a novel treatment for conditions that currently have no treatment technologies available.
• How does healthcare resource use differ between the technology and current care?	Healthcare resource would essentially remain the same for patients using this technology, however better efficacy of care should be achieved.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This treatment should only be used in tertiary care specialist clinics with shared care with secondary care clinicians. The conditions being treated with this technology require specialist monitoring of these disease processes and patient numbers will be limited, therefore the acquired experience of specialists would be required to ensure appropriate use.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Specialist clinicians will need to have some educational CPD on the actual technology and the scope of conditions it can be used in. More importantly understanding of how to titrate medication doses and monitoring of side effects will be paramount.
12. Do you expect the technology to provide clinically	Yes. Clinically meaningful benefits should be seen in terms of:

meaningful benefits compared with current care?	1. BMI SDS loss / weight loss 2. Improved satiety. 3. Improved metabolic outcomes. 4. Secondary improved psychological outcomes around body image and weight.
• Do you expect the technology to increase length of life more than current care?	Some life limitation in POMC deficiency has been due to complications from hypocortisolism that may have been inadequately treated and this would not be resolved through the use of this technology. Nevertheless, although not proven due to a lack of longitudinal data, if weight management in these patients is more successful and patient as a result have better quality of life with reduced or delayed complications, then length of life should potentially increase.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is beneficial for those with abnormal metabolism resulting in early onset obesity cause by abnormalities in the Propriomelanocortin and Melanocortin C pathways and receptors (mainly cause by genetic defects) which are located in the hypothalamus of the brain. Conditions that may include this are MC4R mutations (including LEPR, POMC), Alstrom syndrome.
The use of the technology	
14. Will the technology be easier or more difficult to use	Patients will need to be taught to self-administer the therapy or have a carer administer these daily injections.

for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If patients do not demonstrate improved BMI SDS on treatment for 6 months, then treatment should be discontinued. If patients experience significant side effects, then treatment should also be discontinued.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Yes as there is limited data on effects on quality of life through publications that can assist with the QALY calculation.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is the first targeted therapy for patients with abnormalities in the MC4R pathway. It is an innovative technology and will almost definitely have a substantial impact on patients with these conditions. It will help patients reduce weight far more than other therapies and lifestyle change which has been the only modalities available to such patients until now.
• Is the technology a 'step-change' in the management of the condition?	The technology it novel and should be offered to all patients who have a confirmed diagnosis of a defect in the POMC and MC4R pathway who demonstrate uncontrolled weight gain and early onset obesity, rather than waiting for the assessment and impact of lifestyle change to be assessed first.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. This population currently do not have any therapeutic technological solutions readily available to assist with their condition.
18. How do any side effects or adverse effects of the technology affect the	Previous melanocortin- 4 receptor agonists were found to have important side effects, such as hypertension and increased erections (in adults) however setmelanotide, has had a much improved SE profile and been associated with few, if any, signs of increased blood pressure6 or other adverse effects (Gottesdiener KHC et al , Nat Gen 1998, Kuhnen et al, NEJM 2016).

management of the condition and the patient's quality of life?	Reported SEs of Setmelanotide include dry mouth, nausea and vomiting and occasional mild pain and induration at the injection sites for a few hours during the first few days of treatment. Darkening of skin pigmentation and skin naevi and hair colour may also be noted during administration over time.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Some of the trial have included UK patients and therefore potentially would replicate UK based practice is used here.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Most important outcomes: 1. BMI SDS improvement 2. Improved satiety 3. Improved metabolic outcomes These were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None that I am aware of.
21. How do data on real-world experience compare with the trial data?	I am not certain of this, as this technology has not been used outside of clinical trials as yet in the UK and is certainly not mainstream globally either.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients will need access to a tertiary clinicians and transport to secondary or tertiary units for monitoring and screening. Patients will need to be educated on using a needle based administration device which may be difficult for patients with needle phobia or learning difficulties.

22b. Consider whether these issues are different from issues with current care and why.	I don't feel these issues are significant and have been overcome in a number of other rare conditions or conditions requiring injectable therapies previously.
Topic-specific questions	
23. Would the following treatments be used in this population: a. orlistat b. methylcellulose c. bariatric surgery	1. Orlistat may be trialled in this population however does not improve satiety and may actually have work side effects as a result. 2. Methylcellulose is not routinely used in the paediatric population and again does not improve hyperphagia. 3. Bariatric surgery required in these patients requires more long term procedures such as Roux-en-Y bypass surgery, as due to hyperphagia, gastric banding and gastric sleeve surgery which requires restriction of intake may cause significant side effects. Also weight regain will eventually occur and therefore should be reserved for older patients. Roux-en-Y surgery also results in life-long risk of iron deficiency and other forms of vitamin deficiency and bone health issues.
24. Would you expect people to take setmelanotide in addition to standard care with diet and lifestyle management?	Yes.

25. Would you expect the treatment effect of setmelanotide to differ in people with POMC and LEPR deficiency compared with other genetic deficiencies that result in obesity (such as Bardet-Biedl syndrome, Alström syndrome, Smith-Magenis syndrome and Carboxypeptidase E syndrome)?	Effect in POMC and LEPR patients may be greater than in other patient cohorts. In BBS patients, Setmelanotide in phase 3 trials was shown to cause a 10% reduction in body weight in nearly 40% of cases (N=28) whilst none in the Alstrom group achieved the same. Nevertheless there was a mean reduction from baseline in body weight was -6.2 % and 60% of participants achieved at least 25% reduction in most hunger scores from baseline at approximately 1 year of therapy ($p<0.0001$).(Rhythmn pharmaceuticals, Globe Newswire Dec 2020). Similar results for BBS were found by Haws R et al, Diab Ob Met 2020)
26. How does LEPR or POMC deficiency obesity differ from general obesity? Are outcomes from people with general obesity comparable to the population in this appraisal?	LEPR and POMC deficiency is a genetically driven form of obesity due to uncontrolled hyperphagia and reduced resting metabolic rate due to hypothalamic dysfunction. This is therefore significantly different to general obesity in the population and therefore the general population will not be comparable to patients with these conditions.

27. Does the current treatment for POMC or LEPR deficiency obesity differ in the UK to that in America, Canada and Europe? If so, how?	*LEPR Deficiency in the UK may be treated with recombinant Leptin therapy however there is limited efficacious treatment technologies for POMC deficiency.* There are a number of licensed preparations in the US which are not used in the UK, particularly in the adult population such as combinations preparations Bupropion/Naltrexone, Phentermine /Topiramate (Qsymia), Lorcaserin (Belviq) and GLP1 analogues. However, these preparations as not specifically targeted to the genetic cause of obesity faced by those with POMC and LEPR mutations.
28. How are hyperphagia and BMI associated in LEPR or POMC deficiency obesity? Would you expect: a. The level of hyperphagia to correlate with the severity of the BMI? b. reductions in BMI to improve hyperphagia?	The level of hyperphagia may correlate with severity of BMI, however BMI itself is also affected by resting energy expenditure which is markedly reduced in these patients. Reductions in BMI should correspond with improved hyperphagia but may not have a linear correlation.

29. Would you expect setmelanotide to restore people with LEPR or POMC deficiency obesity to full or near full health?	No. I would expect it to improve their BMI SDS and hyperphagia along with secondary effects on their quality of life in POMC, but I would not expect complete near resolution of the disease phenotype, as seen with Leptin treatment in Leptin deficiency.
30. What are the main differences between LEPR and POMC deficiency? Would you expect the following to differ depending on deficiency type: a. response to long term treatment with setmelanotide? b. BMI and severity of hyperphagia?	Success rates with Setmelanotide treatment in POMC are likely to be higher than in LEPR, however there in inadequate longitudinal data to predict long term responses in these cohorts. Both conditions appear to respond well in terms of BMI SDS reduction and severity of hyperphagia according to phase 2/3 study results.
Key messages	

31. In up to 5 bullet points, please summarise the key messages of your statement.

- Setmelanotide is effective at achieving a reduction in weight in patients with MC4R pathway genetic changes.
- Setmelanotide is effective in reducing hyperphagia in these patients.
- Setmelanotide has some beneficial effect on metabolic outcomes particularly in patients with POMC mutations.
- This technology is the first available targeted therapy for these conditions.
- There are limited other available therapies for these conditions and all have limited effect of improving hyperphagia in particular.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Pooja Sachdev**
2. Name of organisation	**Nottingham Children's Hospital, Nottingham (on behalf of the BSPED)**

3. Job title or position	**Consultant Paediatric Endocrinologist**
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it x☐ other (I am submitting this on their behalf etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The leptin melanocortin system plays an important role in eating behaviours, energy homeostasis and metabolism. Proopiomelanocortin (POMC) is the precursor for melanocyte-stimulating hormone (MSH). The melanocyte-stimulating hormone transmits the anorexic effect of leptin through the melanocortin-4receptor and therefore patients who have a mutation in the gene coding for POMC suffer from early-onset obesity due to severe hyperphagia because of the lack of hypothalamic melanocyte- stimulating hormone. This is a very rare condition. The main aim of treatment is to both reduce weight and prevent/halt further weight gain. Setmelanotide, an eight-amino-acid synthetic cyclic peptide also known as RM-493, is a melanocortin-4 receptor agonist. It provides a mechanism-based treatment of the obesity in proopiomelanocortin deficiency by replacing the absent melanocyte-stimulating hormone that can bind and activate the melanocortin-4 receptor.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	5-10 percent weight loss is quoted as the amount needed to bring about improvement in cardiovascular risk and other co-morbidities. Bariatric surgery consistently provides weight loss in excess of this but is not suitable for everyone and long term data in children and young people is lacking. Studies done so far suggest that the weight loss associated with setmelanotide is in excess of what is considered clinically significant. An investigator- initiated, phase 2, nonrandomized, open-label pilot study of setmelanotide (EudraCT number, 2014-002392-28; ClinicalTrials.gov number, NCT02507492) involving two adult patients with proopiomelanocortin deficiency was conducted and showed that Setmelanotide appeared to completely reverse hyperphagia, and led to significant weight loss (51 kg in patient 1 after 42 weeks and 20.5 kg in patient 2 after 12 weeks) and improvement in their quality of life. The reduction in body weight was like the changes observed after leptin administration in patients with leptin deficiency.

	Further on, greater than 10% weight loss was seen at one year in a phase 3 multicentre trial of Setmelanotide in 10 patients with POMC deficiency in 80% of patients. (Clement K et al, Lancet Diabetes and Endocrinology 2020) In LEPR deficiency, a weight loss >10% was seen in 45% of cases but three quarters of participants reported ≥25% reduction in "most hunger" scores from baseline to ~1 year on therapeutic dose. Only significant reductions in LDL-cholesterol were noted in this cohort (Van de Akker E, Obesity Week 2019).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are very few effective treatments available for the severe obesity and hyperphagia seen in this condition. Therefore, there is a definite unmet need for both patients and health care professionals.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	This condition is currently treated with lifestyle management (calorie reduction and increased activity with reduction in sedentary behaviours), however the degree of obesity is such that this is not enough even in the most motivated individuals. Any complications related to the severe obesity are screened and managed within the NHS.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no specific clinical guidelines for the management of obesity due to LEPR and POMC deficiency and the management is based on protocols used in research. There is NICE Guidance available for the management of obesity per se in both children and adults (CG189)

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care would be determined by the research protocols used. There are <200 patients (fewer than 50 patients with POMC deficiency, 90 with LEPR deficiency and 50 with PCSK1 deficiency reported worldwide so far), so individual experience is sparse and therefore difference of opinion across the NHS is unlikely. .
• What impact would the technology have on the current pathway of care?	Setmelanotide would be the only medical treatment available for these specific genetic conditions causing early onset obesity and hyperphagia. However, there is the potential that it could have a role in those with heterozygous loss of function MC4R mutations as well which make up 1-5 percent of the severe obese population. Weight management of these patients will become more effective, with improvement in cardiovascular risk factors such as dyslipidemia and insulin resistance.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Genetic conditions resulting in early onset severe obesity and hyperphagia do not currently have any specific treatment (except leptin deficiency). Setmelanotide will be used as a new treatment for those diagnosed with LEPR or POMC mutation.
• How does healthcare resource use differ between the technology and current care?	The same health care teams would look after the patient as patients with this degree of severe obesity and the consequent complications are likely to be under secondary/tertiary care. Some additional training and monitoring of side effects would be required but the increased efficacy in care and the resultant reduction in complications would be beneficial both at patient and system level.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As described above, the number of patients with these conditions are very few and therefore centralised Specialist tertiary care with local input would be the best model.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clinicians and their MDT will need training on indications for use, monitoring, and titrating the medication. Ideally all patients should be included in a national/international data base (given the few numbers) to build increased understanding of its use and long-term effects.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Clinically meaningful benefits will include weight loss, reduced hyperphagia, decreased cardiovascular risk and complications associated with severe obesity (fatty liver/obstructive sleep apnoea) as well as improved Quality of life.
• Do you expect the technology to increase length of life more than current care?	Yes, weight reduction and consequent reduction in associated co-morbidity would potentially increase longevity.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This has been shown in the research studies as well.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is targeted at those who have a defect in the MC4R pathway -specifically and would be less effective in those whose severe obesity is due to other causes. However, this is a new emerging field and other conditions in whom early onset obesity and hyperphagia is a feature may also benefit once this is established.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Patients and their families/carer if needed will need to be taught to do the injections. A number of these patients may already be on treatments necessitating injections. Additional monitoring for side effects may be needed but these patients are likely to be under regular monitoring anyway due to their severe obesity and associated comorbidities.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Reduction in BMI SDS is expected soon after the onset of therapy, therefore if no change is seen within 6 months, treatment should not be continued.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, this technology is innovative and has the potential to make significant and substantial impact on health-related benefits. The weight loss seen in these trials is in excess of that seen with other therapies and the significant lifestyle changes with severe permanent restrictions on food intake are very difficult to sustain even in the most motivated individuals.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, this technology is a 'step change' in the management of this condition and will result in significant improvement.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. There is no targeted treatment available for those with POMC or LEPR deficiency currently.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	First generation MC4R agonists resulted not only in suppression of food intake and induction of weight loss, but also in a significant increase in blood pressure (BP) and heart rate (HR) in rodents, primates, and humans. For example, treatment of obese volunteers with the agonist LY2112688 at the maximum dose of 1.0 mg/day led to significant increases of systolic (mean 9.3 SD 1.9 mmHg) and diastolic (mean 6.6 SD 1.1 mmHg) blood pressure after only 24 h of treatment compared with placebo. These adverse effects halted the development of the first generation of MC4R agonists. (Greenfield et al 2009 NEJM). In the open label, multicenter trial of 21 participants, the most common adverse events were injection site reaction and hyperpigmentation, which were reported in all ten participants in the POMC trial; nausea was reported in five participants and vomiting in three participants. In the LEPR trial, the most commonly reported treatment-related adverse events were injection site reaction in all 11 participants, skin disorders in five participants, and nausea in four participants. No serious treatment-related adverse events were seen (Clement et al 2020 lancet Diabetes and Endocrinology). The risks of the condition far outweigh the reported side effects.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, UK patients were part of the trial.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Most important outcomes are weight loss, reduction in hyperphagia and improved co-morbidity-all of these are addressed in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None that I am aware of.
21. How do data on real-world experience compare with the trial data?	I am not aware that anyone has tried this outside of clinical trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	As it is injectable, people with vision problems, learning difficulties, physical disability and needle phobia will need support to access this technology but support should already be in place to manage their other health needs.
22b. Consider whether these issues are different from issues with current care and why.	The benefit of treatment far outweighs the time/effort and resources required to address these issues.
Topic-specific questions	

23. Would the following treatments be used in this population: a. orlistat b. methylcellulose c. bariatric surgery	a) Orlistat can be used, however weight loss quoted is an average of 6 kg and while any weight loss is helpful, this may not be clinically meaningful in populations with such severe obesity. Adherence is also poor due to side effects. b) Methylcellulose is not routinely used in paediatrics. c) Bariatric surgery in this specific group of patients with homozygous variants of the leptin/melanocortin pathway is less effective as they are at high risk of putting the weight back on due to their hyperphagia and baseline primary energy balance disorder. The follow up is variable and outcomes are generally disappointing. (Le Beyec J 2013 JCEM, MI Cooiman 2020 Obesity Surgery, Y Li 2019 Obesity Surgery). The outcomes with those who have heterozygous variants is better though choice of procedure is also important (bypass versus sleeve) (MI Cooiman 2020 Obesity Surgery). Overall, long term outcomes of bariatric surgery in paediatric populations is still lacking.
24. Would you expect people to take setmelanotide in addition to standard care with diet and lifestyle management?	Yes.
25. Would you expect the treatment effect of	Effect in POMC and LEPR patients may be greater than in other patient cohorts.

setmelanotide to differ in people with POMC and LEPR deficiency compared with other genetic deficiencies that result in obesity (such as Bardet-Biedl syndrome, Alström syndrome, Smith-Magenis syndrome and Carboxypeptidase E syndrome)?	In a study, looking at setmelanotide in Bardet- Beidel syndrome, 10 individuals were recruited to a study and seven completed it. Mean percent change in body weight from baseline to 3 months was −5.5% (90% CI, −9.3% to −1.6%; n = 8); change from baseline was −11.3% (90% CI, −15.5% to −7.0%; n = 8) at 6 months and −16.3% (90% CI, −19.9% to −12.8%; n = 7) at 12 months. All participants reported at least one treatment- emergent adverse event (AE), most commonly injection-site reaction. No AEs led to study withdrawal or death. Most, morning, and average hunger scores were reduced across time points. (Haws et al 2020)
26. How does LEPR or POMC deficiency obesity differ from general obesity? Are outcomes from people with general obesity comparable to the population in this appraisal?	No, outcomes from people with general obesity are not comparable though as more information becomes available, it maybe those other genetic mutations resulting in severe obesity may also be targeted if a part of the same pathway. The obesity in LEPR and POMC deficiency is due to a rare genetic defect due to severe hyperphagia and reduced resting metabolic rate due to hypothalamic dysfunction.
27. Does the current treatment for POMC or LEPR deficiency obesity differ in the UK to that	GLP1 analogues are now licensed for type 2 diabetes in children and young people and off license use in severe obesity is a potential. Other drugs being used in adult obesity are not licensed in the UK. However,

in America, Canada and Europe? If so, how?	these preparations as not specifically targeted to the genetic cause of obesity faced by those with POMC and LEPR mutations.
28. How are hyperphagia and BMI associated in LEPR or POMC deficiency obesity? Would you expect: a. The level of hyperphagia to correlate with the severity of the BMI? b. reductions in BMI to improve hyperphagia?	The increased BMI is due both to reduced resting energy expenditure and the hyperphagia. Direct corelation between the hyperphagia and BMI is difficult to show. A decrease in BMI would correspond with improved hyperphagia as seen in the open label studies but this effect is not sustained once the medication is stopped (Peter Kuhnen 2016 NEJM). This has also not been see consistently in patients who have lost weight following bariatric surgery.
29. Would you expect setmelanotide to restore people with LEPR or POMC	No. I would not expect for them to be restored to full health as the degree of obesity is extreme. However, reducing complications and co-morbidity risk will have a significant impact on QoL.

deficiency obesity to full or near full health?	
30. What are the main differences between LEPR and POMC deficiency? Would you expect the following to differ depending on deficiency type: a. response to long term treatment with setmelanotide? b. BMI and severity of hyperphagia?	Based on the open label study, weight loss with Setmelanotide treatment in POMC was seen in a larger number of patients (80 % versus 45%) than in LEPR, however there is not enough long term data to predict outcomes. All patients being offered this medication should be followed up longer term and having a national/international dashboard for clinicians to submit outcomes should be considered to build the evidence. Both conditions appear to respond well in terms of BMI SDS reduction and severity of hyperphagia according to phase 2/3 study results.
Key messages	

31. In up to 5 bullet points, please summarise the key messages of your statement.

- Setmelanotide is effective in bringing about clinically significant weight loss in patients with MC4R pathway genetic changes.
- Setmelanotide also reduces the reducing hyperphagia in these conditions.
- The adverse effects are tolerable and the risks of the condition far outweight these.
- There are very few treatment options for patients with these extremely rare genetic syndromes.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor I. Sadaf Farooqi**
2. Name of organisation	**University of Cambridge and Addenbrooke's Hospital, Cambridge, UK**

3. Job title or position	**Professor of Metabolism and Medicine and Honorary Consultant Physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	These two genetic conditions cause hyperphagia (sustained drive to eat) and severe obesity that begins in early childhood, is associated with increased risk of mortality (due to associated infections) and causes life-long severe obesity with impaired mobility, type 2 diabetes and other health problems. Severe childhood-onset obesity significantly impairs quality of life, educational and job opportunities. There is currently no effective treatment for these 2 conditions. Diet, activity and currently available medical therapies (Orlistat) are seldom effective; bariatric surgery is contra-indicated as it doesn't tackle the cause of obesity which is disordered function of the hypothalamus. The main aim of treatment is to achieve clinically significant weight loss, thereby improving mobility, co-morbidities and quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant treatment response would be weight loss of at least 5% of baseline weight.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is no effective treatment for these disorders so there is an unmet need.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	These conditions are very rare. UK patients have been assessed by me (In Cambridge) and are followed up jointly with their local Physicians.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No clinical guidelines for the treatment of these conditions exist. A consensus conference was recently held (World Obesity Federation, 2021) to develop recommendations in genetic obesity syndromes. (I chaired this; it will recommend that based on the Phase 3 trial data Setmelanotide should be offered to patients with these two genetic conditions).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	To be honest, I am the only professional with experience of managing patients with both conditions in the UK. These are very rare disorders. The pathway of care is not well-defined; the mainstay has been supportive treatment alongside treatment of complications (e.g. type 2 diabetes as they arise). I have also seen and assessed patients from outside the UK and contributed to their clinical management.
• What impact would the technology have on the current pathway of care?	The technology would substantially improve the clinical care of patients with these two rare conditions. It would allow for a pathway to be defined (genetic diagnosis leads to treatment delivered in a specialist centre with experience with additional support delivered locally).
11. Will the technology be used (or is it already used) in	There is no current pathway in the NHS. A new pathway would improve clinical care for these rare patients.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology is likely to improve health, reduce morbidity and thus reduce the health care costs associated with treating patients with severe obesity due to these rare disorders.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary specialist centres only –these are very rare conditions (less than 20 patients in the UK).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal as technology can be delivered alongside existing clinical services (in a Endocrine clinic).
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – there is no current treatment. The technology is the first effective treatment for these two disorders and targets the mechanism that causes the obesity in these patients.
• Do you expect the technology to increase	Yes – both conditions are associated with reduced life expectancy due to severe obesity.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – quality of life is poor as children develop severe obesity from the first year of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is targeted at a very specific group of patients with rare genetic disorders. These are the patients in whom it is most likely to be effective.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	There is no current care/effective treatment. For the technology, patients need to be taught to administer subcutaneous injections. There are no concomitant medications or need for additional monitoring.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If the treatment does not result in clinically significant weight loss (> 5%) after 6 months, then in line with other weight loss medications, it would be reasonable to stop treatment. Monitoring of weight is sufficient to inform this decision.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Based on my knowledge of these conditions and other genetic disorders causing severe obesity which we treat (congenital leptin deficiency), I think the treatment is likely to significantly improve quality of life by improving mobility and medical conditions, but also improving confidence, self-esteem, reducing stigma and increasing engagement with education and employment. The latter may not be fully captured in a QALY calculation.
17. Do you consider the technology to be innovative in	Yes, its innovative – it targets the mechanism causing the obesity. As above.

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – since these disorders were discovered in 1998 there has been no treatment. Many patients globally (referred to me for genetic diagnosis) have died. This is transformative for the care of patients with these rare disorders.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. As above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main adverse effect is pigmentation. To date, most patients seem to tolerate this well.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	There is no formal current UK care pathway. The approach used in the trials could readily be implemented in the NHS as not too onerous.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Most important outcomes, loss of weight and reduction in hunger (they were measured).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
20. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Align (improvements in quality of life are not captured by the trial data reported to date. I am aware of a qualitative study that is likely to be published soon)
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Of note, these are bi-allelic, recessive disorders, so disproportionately affect people from ethnic backgrounds where consanguineous marriage is more commonly practised.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Would the following treatments be used in this population:	

a. orlistat b. methylcellulose c. bariatric surgery	No – a) and b) cause only minor weight loss and do not work in severe obesity due to genetic conditions. c) can result in some weight loss, but as it doesn't tackle the cause of the problem and hyperphagia remains it is not advised in these conditions.
24. Would you expect people to take setmelanotide in addition to standard care with diet and lifestyle management?	Yes.
25. Would you expect the treatment effect of setmelanotide to differ in people with POMC and LEPR deficiency compared with other genetic deficiencies that result in obesity (such as Bardet-Biedl syndrome, Alström syndrome, Smith-Magenis syndrome and	I would expect Setmelanotide to be effective in all these conditions, but, in line with the published trial experience, I would expect it to be more effective in POMC and LEPR deficiencies (because they impact more clearly on the melanocortin pathway and so these patients are likely to see a larger weight loss response).

Carboxypeptidase E syndrome)?	
26. How does LEPR or POMC deficiency obesity differ from general obesity? Are outcomes from people with general obesity comparable to the population in this appraisal?	This is very different. Obesity starts before the age of 1 year. Patients on average weigh 26 kg at age 2, 45 kg at age 5, 110 kg at age 10 years etc. Outcomes are worse in this group. Based on global experience, mortality in childhood is high (> 25% in LEPR deficiency).
27. Does the current treatment for POMC or LEPR deficiency obesity differ in the UK to that in America, Canada and Europe? If so, how?	No. there is no other current treatment globally. Setmelanotide has been approved by the FDA and EMA in 2020/2021.
28. How are hyperphagia and BMI associated in LEPR or POMC deficiency obesity? Would you expect:	Hyperphagia (increased and sustained drive to eat) is severe and the major cause of obesity. Reduced ability to burn fat (due to impaired sympathetic tone) also contributes to obesity. Setmelanotide reduces the hyperphagia and accelerates burning of fat, both of which in turn lead to weight loss.

a. The level of hyperphagia to correlate with the severity of the BMI? b. reductions in BMI to improve hyperphagia?	
29. Would you expect setmelanotide to restore people with LEPR or POMC deficiency obesity to full or near full health?	I would expect substantial weight loss (more so in POMC than LEPR deficiency). They may remain overweight/obese depending on starting weight and other clinical factors.
30. What are the main differences between LEPR and POMC deficiency? Would you expect the following to differ depending on deficiency type:	As above. Setmelanotide effectively replaces POMC so I would expect a greater effect on hunger and BMI in POMC deficiency (as also seen in the trials).

a. response to long term treatment with setmelanotide? b. BMI and severity of hyperphagia?	

Key messages

31. In up to 5 bullet points, please summarise the key messages of your statement.

- very rare disorders – less than 20 patients in the UK
- diagnostic system (NHS genetic services) well established (numbers unlikely to increase much with wider testing).
- this is the only effective treatment for these conditions for which no treatment exists and mortality in childhood is high.
- safe and well-tolerated, easy to incorporate into clinical care (specialist centre in NHS)
- potential to transform the care of these patients and substantially improve education and quality of life

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Alexander William Potter**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Prof. Farooqi, Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Think of a time when you, the reader, have been hungry. In fact, not just hungry; but famished. Remember the effort it took to concentrate on anything but food. Now imagine trying to live, to function, to thrive whilst that knot – that pain – in your stomach persists for every waking moment of your day. Physical difficulties: • Restricted movement; exercise • Losing weight • Off the peg clothes do not fit • Only partial pubertal development Emotional difficulties: • Bullying • Social integration • People look at my belly before they look at me Life: • Unfavourable coping methods • Few friends • Restriction of opportunities • Progress through education • Resulting limitations to career

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Educational treatments – diets, lifestyle advice, weight management programmes, etc. – are not sustainable or effective on a long-term basis. Hyperphagia, essentially a basic survival instinct, is as powerful as the need to breathe and sleep. It will always either overrule the mind or limit ability during the fight against it. Similarly, I understand the principle of a gastric band is that it allows time for messages from the stomach to reach the brain by reducing the volume of food one can consume in any given period. The somewhat obvious flaw in the use of this treatment for a patient in the context being discussed here is that the message from the stomach will never reach its intended target.
11. Is there an unmet need for patients with this condition?	• Awareness of the disease • Explanation of the disease to patients • Inclusion of patients on the trial, although I appreciate that restrictions apply • Mental health support
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an	• Reduced/no hunger – life does not revolve around food • Weight loss – healthier – reduced risk of weight induced illnesses • Improved physical ability • Improved confidence • The ability to lead a life in which the results of one's choices are proportional • Equity in educational, work, and social lives • Improved mental health – reduced likelihood of adverse side effects • Increased medical capacity to care for other patients

affected child, please also include their improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	Excluding pain as a barrier, administering treatment is easy. A steady hand, the ability to count, and access to a permanently cold storage location is all that's needed. Alternatively, a willing and trusted volunteer with the aforementioned attributes could be employed. Some patients may struggle with elements of the process, however; perhaps trypanophobia, perhaps algophobia, perhaps a low pain threshold. Occasionally there are disadvantages (see below), but one soon gets used to them. To conclude, the advantages far outweigh the disadvantages.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they,	• Insertion of needles can cause temporary pain. • Bruising around injection sites, where once a month it may last for 7-10 days. Tolerable and of no consequence to daily activity. • Aching of joints during the initial introduction of treatment. • Occasional headaches, often due to dehydration through reduced hyperphagia and thus, consumption. "Occasional" is subjective to each patient's journey. • Significant darkening of the skin and hair, although this could be considered an advantage.

how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	• Random, often untimely erections When travelling beyond where the treatment is usually kept, these can be difficult: • Finding a fridge/ using cooling facilities • Finding privacy • Explaining what the treatment is, why you need it, and why it isn't going to blow a plane up (keeping a letter from your medical professional with the treatment helps with that one)… all in all, dealing with people Whilst on the trial, I have used a significant proportion of my annual leave to attend mandatory medical appointments. This has not been financially compensated but whilst that would be nice, the wider aim of helping untreated and undiagnosed patients through this treatment's approval is of much greater importance. The only time my family has been disadvantaged is when I forgot to take needles with me on a weekend trip – half of it was lost visiting pharmacies and hospitals! I believe that there are no aspects of the condition that the treatment does not help with or makes worse, nor have I or my family been out of pocket as a result of this treatment. On the contrary, I spend much less on food than I did pre-treatment.
Patient population	
15. Are there any groups of patients who might benefit more or less from the	Younger patients may benefit more than others owing to the reduction in impact of the disease and subsequent increased number of opportunities, or rather the return of opportunities afforded to those

treatment than others? If so, please describe them and explain why.	without the disease. However, again, benefits are subjective and no matter when in a patient's life treatment is received, it will improve.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	In terms of delivery of the treatment, no, for patients with the disease suffer the same physical effects. However, the environments patients live in influence variable factors that lead to differing outcomes from treatment. When comparing obesity or the treatment of, regardless of its cause, consideration should therefore be given to a range of factors, not only 'hard' data. Read 'hard' as numbers on a chart without regard for context. Unlike the cause of many other diseases, increased calorie intake – simply put, food – is linked in some manner to all seven measures of deprivation within the nationally recognised Indices of Multiple Deprivation: Income, Employment, Education, Health, Crime, Barriers to Housing and Services, and Living Environment.
Other issues	
17. Are there any other issues that you would like the committee to consider?	None
Topic specific questions	
18. Please list all the healthcare resources/medical	• Daily use of Setmelanotide in accordance with my care plan. • Quarterly check-ups with Prof. Farooqi at Addenbrooke's Hospital, University of Cambridge.

appointments that you or the child you care for use/attend.	

Key messages

19. In up to 5 bullet points, please summarise the key messages of your statement:

- Hyperphagia is a cloud that shadows each and every moment of life. Setmelanotide removes that shadow – it provides equity. Anyone can choose to act – or to not – but only patients receiving treatment are afforded fair results compared to people without the disease. Being born with this disease vs being born without it can be the difference between accessing education and not. Being fat vs being fit can be the difference between living in poverty and living in privilege. Exercising with Setmelanotide vs exercising without it **IS** the difference between losing mass and not. Without Setmelanotide – without equity – patients will continue to suffer disadvantage.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**DEBBIE POTTER**
2. Are you (please tick all that apply):	☐ a patient with the condition? **X** a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Professor Sadaf Farooqi
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't **X** I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised X I have other relevant personal experience. I am Alex's mother ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	Alex was born in 1994, prior to the discovery of LEPR. Therefore, there was absolutely no information or treatment available at that time. After being accepted on the research program when Alex was 4, it took a further 6 years before we received a diagnosis that Alex had a genetic mutation. The only information we received at that time was an explanation that "the message doesn't reach his brain to tell him he is full". No support was offered and no further contact was received until Alex was 21. The impact on me personally, was both physically and mentally demanding. By 9 months he weighed the same as a 2 yr old and by 2 yrs he weighed that of an 8 yr old. I struggled physically to lift him. My obsession in trying to find answers and the anxiety caused around people giving him food, negatively affected close relationships. There was no professional or medical support offered which I now believe was partly due to ongoing research and the medical practitioners lack of knowledge and understanding around genetic obesity.

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Alex outgrew nappies early on so I bought adult incontinence pads which weren't sufficiently absorbent, resulting in having to change his bed sheets every night. We had to get an orthopaedic buggy on medical loan as every pushchair broke due to his size. My mother made all his clothes as nothing would fit him. I had to buy shoes 2 sizes too big to fit his feet. Insatiable appetite. He would steal food and eat at every opportunity. Hunger was all consuming. I made his food from scratch to give best nutritional value whilst restricting calorie intake to try and stabilise weight gain. We kept Alex as distracted/active as possible. Walking to/from school, football, rugby, swimming, karate, scouts. Regular hospital visits became traumatic when he had to have another blood test and they couldn't find a vein because of the fat. All of the above had a significant financial and emotional impact. LepR affected Alex's levels of testosterone hormone during puberty which affected normal growth. If there had been a diagnosis/treatment earlier Alex would have reached his development potential.

	On reflection and in hindsight, life was extremely challenging at times but Alex was a happy child, did well at school and this was our normal so we knew no different. Alex struggled with his emotional wellbeing when he started senior school. He was bullied, had few friends and became difficult to live with. I lost control over what he ate and he gained 1 stone/year. We constantly argued over his weight and our relationship suffered. I was convinced he would die young due to the pressure on his vital organs or as a result of his mental health. Alex was always a high achiever but messed up his A levels as he couldn't face going to university. The impact of LepR is enormous
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	There are no current treatments available.

11. Is there an unmet need for patients with this condition?	yes
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	• The ability to live a normal life: • Not feeling permanent hunger resulting in weight loss • Improved relationship with food – enjoying food as a pleasurable experience rather than the necessity of living out of the fridge trying to satisfy all consuming insatiable hunger • Improved mental wellbeing/self-esteem eg Strangers look Alex in the eye now rather than look at his belly first • being able to buy clothing “off the peg” rather than limited XXXL • Improved physical ability • This treatment has been truly life changing

13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	Setmelanotide has to be injected daily. Alex was 21 when he started the trial so has always administered this himself. When travelling, he has to carry medical documentation to explain why he is carrying the drug. It also has to be kept at a certain temperature which can prove tricky on occasion.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any	From a carer's perspective I can't see any disadvantages of Setmelanotide. Alex has only experienced 2 positive side effects. • He no longer feels hunger • Darker pigmentation in skin/hair colour Resulting in social acceptance – change in society's perception/unconscious bias – no longer pale, fat and ginger!

disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Given our experience, I can't see that any group would not benefit from the treatment. I feel that younger patients/carers would benefit more from an early diagnosis and treatment as they would be able to lead a normal life sooner, and would not have to go through the trauma we experienced. Needle phobic patients may experience increased anxiety, but I feel the benefits far outweigh any potential negative
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	I do not see any potential equality issues.

Other issues	
17. Are there any other issues that you would like the committee to consider?	None
Topic specific questions	
18. Please list all the healthcare resources/medical appointments that you or the child you care for use/attend.	Alex uses Setmelanotide daily and has quarterly check-ups with Professor Farooqi at Addenbrooke's Hospital, University of Cambridge
Key messages	

19. In up to 5 bullet points, please summarise the key messages of your statement:

- Setmelanotide is life changing
- Setmelanotide enables patients and carers to lead a normal life
- Setmelanotide improves quality of life and in my opinion life expectancy
- Achievement is not restricted by physical limitation, emotional wellbeing or unconscious bias
- Setmelanotde improves self-esteem and mental wellbeing which results in healthier personal relationships

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

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

Highly Specialised Technologies Evaluation Programme

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Authors

Amanda Brand[1]
Madhusubramanian Muthukumar[1]
Maxwell S Barnish[1]
Brian O'Toole[1]
Laura Trigg[1]
Sophie Robinson[1]
Tricia Tan[2]
Stephen O'Rahilly[3]
G.J. Melendez-Torres[1]
Louise Crathorne[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter

[2] Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London

[3] Wellcome-MRC Institute of Metabolic Science, University of Cambridge

Correspondence to

Amanda Brand

3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; a.brand2@exeter.ac.uk

Date completed

08/09/2021 (ACIC marking revised January 2022)

Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/35/94.
Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows	Brand, Muthukumar, Barnish, O'Toole, Trigg, Robinson, Tan, O'Rahilly, Melendez-Torres, Crathorne. Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]: A Highly Specialised Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2021.

Author Contributions:	
Amanda Brand	Project lead, critical appraisal of the company submission, writing and editorial input
Madhusubramanian Muthukumar	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Maxwell S Barnish	Lead for the ERG's appraisal of the clinical evidence, drafted clinical sections of the report, writing and editorial input
Brian O'Toole	Lead for the ERG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
Laura Trigg	Critical appraisal of the clinical evidence and drafted sections of the report
Sophie Robinson	Critical appraisal of the literature search strategies, conducted additional literature searching, and editorial review
Tricia Tan	Clinical advice and review of draft report
Stephen O'Rahilly	Clinical advice and review of draft report
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report
Louise Crathorne	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report

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 0, 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 0, 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 0, 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 0, 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 0, 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 0, 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 0, 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 6 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 6.
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:

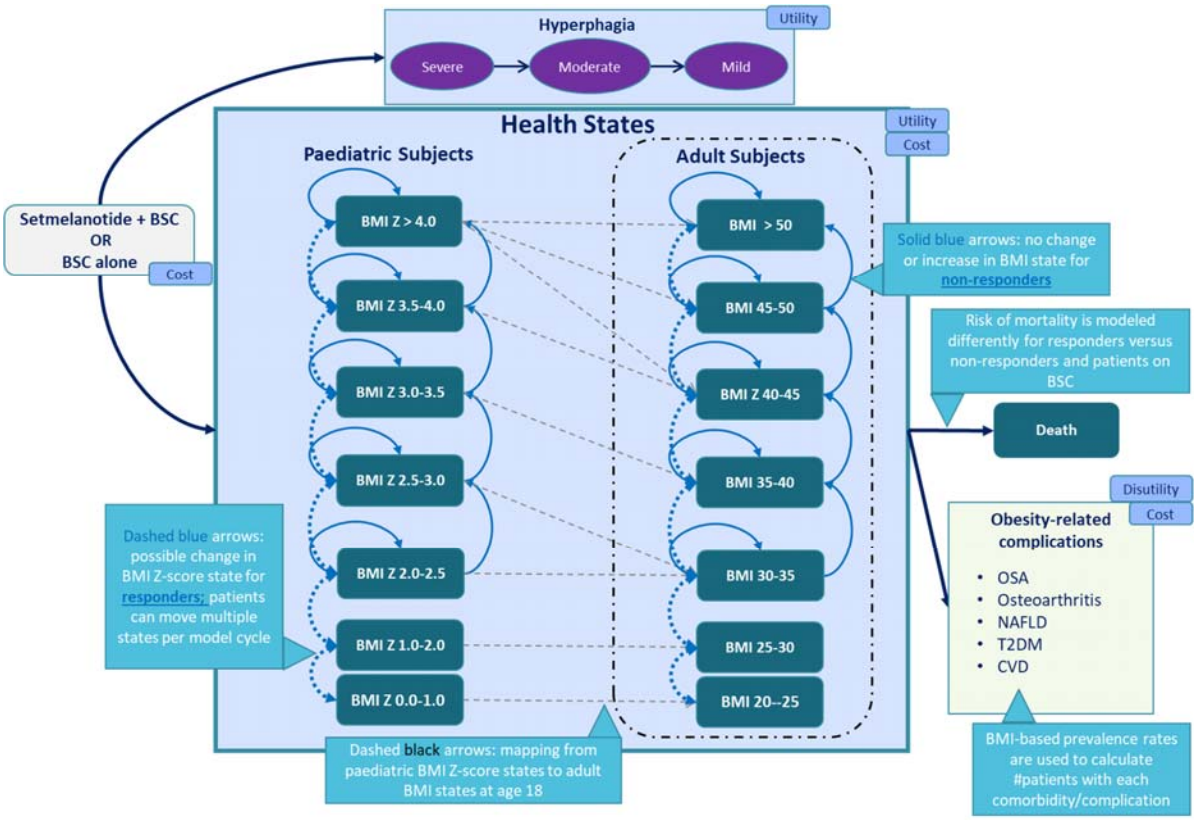
- During the clarification stage, the ERG queried the company's rationale for deviating from the model structure reported in Ara et al. 2012[46], a systematic review of clinical and cost effectiveness of using drugs in treating obese patients in primary care, which informed the model structure in some 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). 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

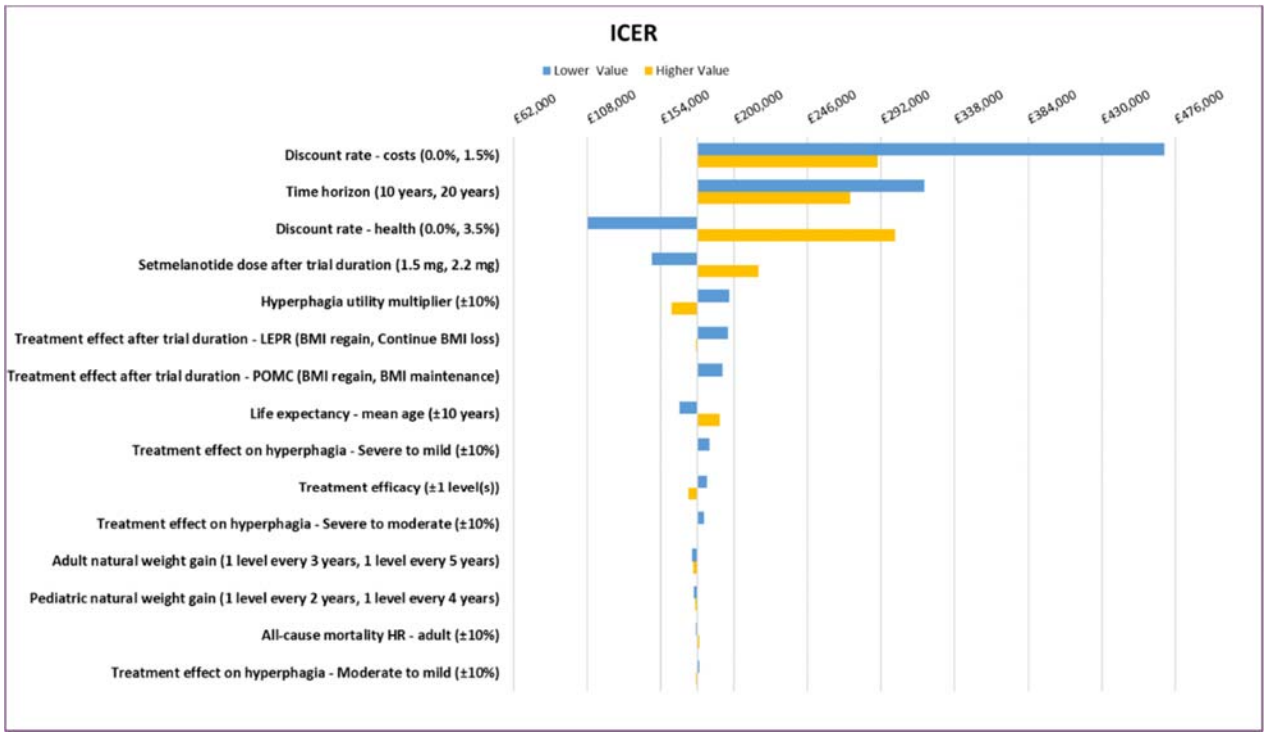
5.1.3. Company's sensitivity analyses

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.

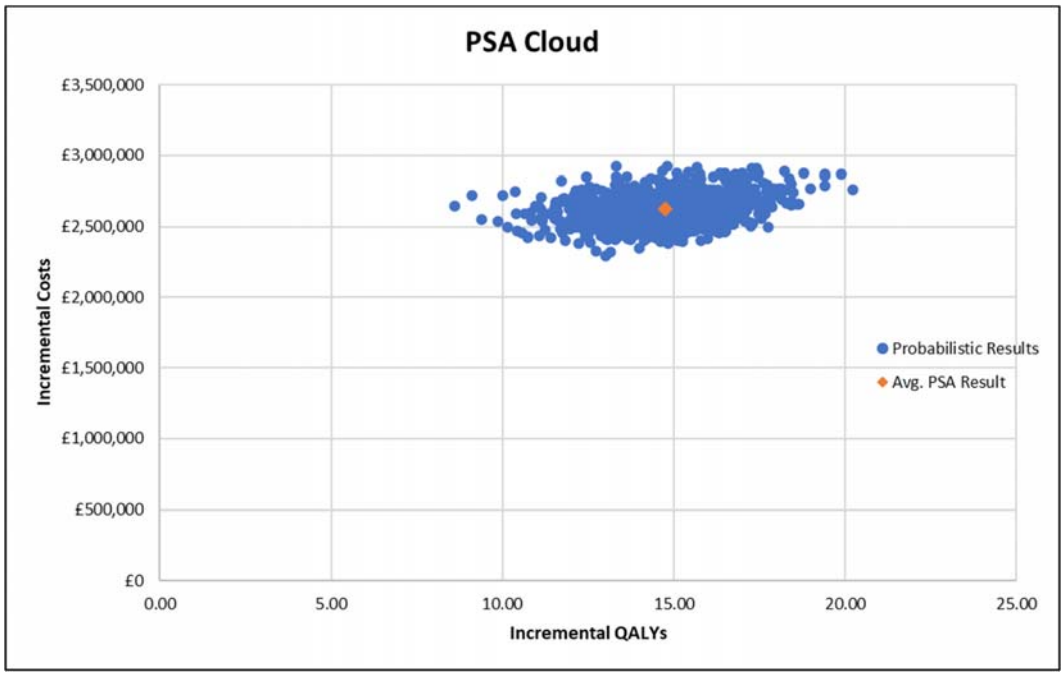
Table 35. Model parameters which were not included in the PSA

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

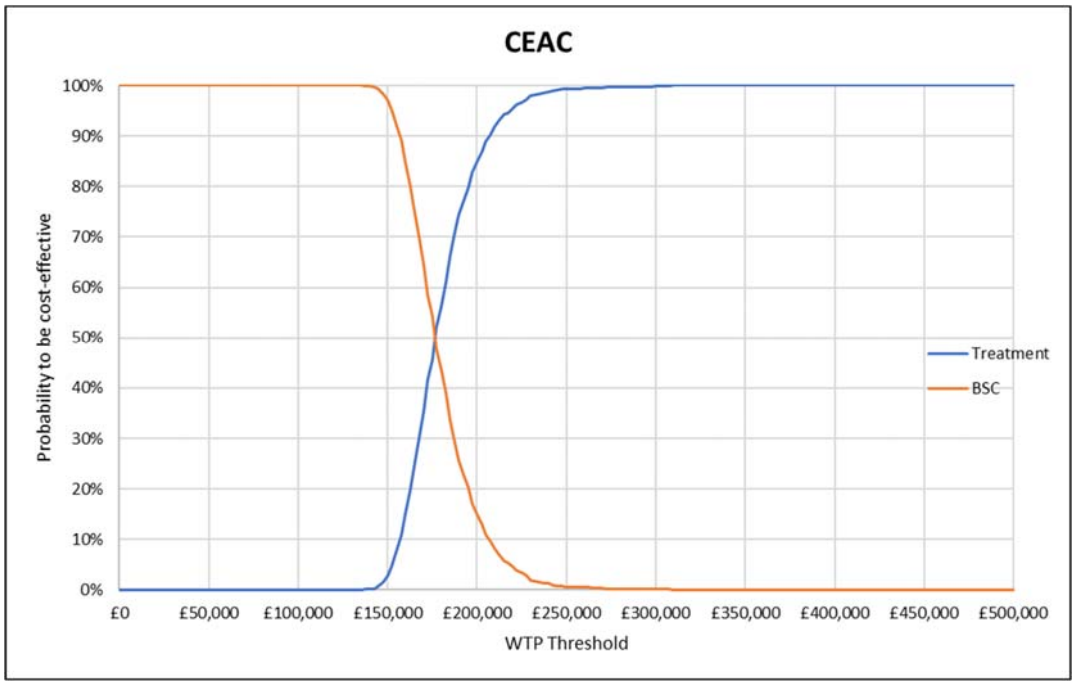
- Within the cost-effectiveness acceptability curve (CEAC) it was noted the maximum willingness to pay to be £500,000. However, within the interim process and highly specialised technologies programme, it specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised 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	Incremental life years	Incremental QALYs	Incremental costs	Cost per QALY gained
Scenario 9	[redacted]	[redacted]	[redacted]	£177,134
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.

References

1. Eneli I, Xu J, Webster M, McCagg A, Van Der Ploeg L, Garfield AS, et al. Tracing the effect of the melanocortin-4 receptor pathway in obesity: study design and methodology of the TEMPO registry. Appl Clin Genet [Internet]. 2019 2019; 12:[87-93 pp.]. Available from: http://europepmc.org/abstract/MED/31239751

https://doi.org/10.2147/TACG.S199092

https://europepmc.org/articles/PMC6556479

https://europepmc.org/articles/PMC6556479?pdf=render.

2. Cansell C, Denis RGP, Joly-Amado A, Castel J, Luquet S. Arcuate AgRP neurons and the regulation of energy balance. Front Endocrinol (Lausanne) [Internet]. 2012 2012; 3:[169 p.]. Available from: http://europepmc.org/abstract/MED/23293630

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23293630/pdf/?tool=EBI

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23293630/?tool=EBI

https://doi.org/10.3389/fendo.2012.00169

https://europepmc.org/articles/PMC3530831

https://europepmc.org/articles/PMC3530831?pdf=render.

3. Frihauf JB, Zorrilla EP, Fekete EM. Control of Food Intake. In: Koob GF, Moal ML, Thompson RF, editors. Encyclopedia of Behavioral Neuroscience. Oxford: Academic Press; 2010. p. 335-44.

4. Nunziata A, Funcke JB, Borck G, von Schnurbein J, Brandt S, Lennerz B, et al. Functional and Phenotypic Characteristics of Human Leptin Receptor Mutations. J Endocr Soc. 2019;3(1):27-41.

5. Ayers KL, Glicksberg BS, Garfield AS, Longerich S, White JA, Yang P, et al. Melanocortin 4 Receptor Pathway Dysfunction in Obesity: Patient Stratification Aimed at MC4R Agonist Treatment. J Clin Endocrinol Metab. 2018;103(7):2601-12.

6. Adan RAH, Tiesjema B, Hillebrand JJG, la Fleur SE, Kas MJH, de Krom M. The MC4 receptor and control of appetite. British Journal of Pharmacology. 2006;149(7):815-27.

7. Kleinendorst L, Abawi O, van der Kamp HJ, Alders M, Meijers-Heijboer HEJ, van Rossum EFC, et al. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. European Journal of Endocrinology. 2020;182(1):47-56.

8. Stijnen P, Ramos-Molina B, O'Rahilly S, Creemers JWM. PCSK1 Mutations and Human Endocrinopathies: From Obesity to Gastrointestinal Disorders. Endocrine Reviews. 2016;37(4):347-71.

9. Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O'Rahilly S. Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene. New England Journal of Medicine. 2003;348(12):1085-95.

10. Kleinendorst L, van Haelst MM, van den Akker ELT. Genetics of Obesity. Exp Suppl. 2019;111:419-41.

11. NHS. Obesity Overview 2021. Available from: https://www.nhs.uk/conditions/obesity/.

12. NICE. Clinical guideline [CG189] Obesity: identification, assessment and management 2014. Available from: https://www.nice.org.uk/guidance/cg189.

13. Challis BG, Millington GWM. Proopiomelanocortin Deficiency – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle

14. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. New England Journal of Medicine. 2007;356(3):237-47.

15. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health. 2009;9(1):1-20.

16. Narang I, Mathew JL. Childhood obesity and obstructive sleep apnea. Journal of nutrition and metabolism. 2012;2012.

17. Selvakumar PKC, Kabbany MN, Alkhouri N. Nonalcoholic fatty liver disease in children: not a small matter. Pediatric Drugs. 2018;20(4):315-29.

18. Aykut A, Özen S, Gökşen D, Ata A, Onay H, Atik T, et al. Melanocortin 4 receptor (MC4R) gene variants in children and adolescents having familial early-onset obesity: genetic and clinical characteristics. European journal of pediatrics. 2020:1.

19. Hilbert A, Rief W, Braehler E. Stigmatizing attitudes toward obesity in a representative population-based sample. Obesity. 2008;16(7):1529-34.

20. FDA. Genentech. XENICAL (orlistat) US Prescribing Information. 2015.

21. Qsymia. VIVUS. QSYMIA (phentermine and topiramate extended-release) US Prescribing Information: QSYMIA webpage. 2018.

22. FDA. Pharmaceuticals C. CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) US Prescribing Information FDA webpage. 2020.

23. FDA. Nordisk N. SAXENDA (liraglutide) US Prescribing Information FDA webpage. 2020.

24. NICE. NICE guideline [NG7] Preventing excess weight gain. 2015.

25. NICE. Clinical guideline [CG43] Obesity prevention 2006. Available from: https://www.nice.org.uk/guidance/cg43.

26. Beaumont KA, Wong SS, Ainger SA, Liu YY, Patel MP, Millhauser GL, et al. Melanocortin MC_1 receptor in human genetics and model systems. Eur J Pharmacol. 2011;660(1):103-10.

27. Kanti V, Puder L, Jahnke I, Krabusch PM, Kottner J, Vogt A, et al. A Melanocortin-4 Receptor Agonist Induces Skin and Hair Pigmentation in Patients with Monogenic Mutations in the Leptin-Melanocortin Pathway. Skin Pharmacol Physiol. 2021:1-10.

28. NICE. Setmelanotide for treating obesity caused by LEPR or POMC deficiency

[ID3764] - final scope. NICE, ; 2021.

29. Poitou C, Puder L, Dubern B, Krabusch P, Genser L, Wiegand S, et al. Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes. Surgery for Obesity and Related Diseases. 2021.

30. Centre for Reviews and Dissemination. Systematic reviews. CRD's guidance for undertaking reviews in health care. . University of York; 2008.

31. CASP. Critical Appraisal Skills Programme (CASP) checklists. . Available from: http://www.casp-uk.net/casp-tools-checklists.

32. Higgins JP AD. Chapter 8: Assessing risk of bias in included studies. . In: Higgins JP GS, editor. Cochrane Handbook for Systematic Reviews of Interventions Version 510 The Cochrane Collaboration, ; 2011.

33. Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. N Engl J Med. 2016;375:240-6.

34. Clément K, Biebermann H, Farooqi IS, Van der Ploeg L, Wolters B, Poitou C, et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. Nature medicine. 2018;24(5):551-5.

35. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. The Lancet Diabetes & Endocrinology. 2020;8(12):960-70.

36. Register EUCT. Long Term Extension Trial of setmelanotide (RM-493) 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 2017. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000387-14/DE.

37. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: extension to randomised crossover trials. BMJ. 2019;366:l4378.

38. Freeman PR. The performance of the two-stage analysis of two-treatment, two-period crossover trials. Stat Med. 1989;8(12):1421-32.

39. NICE. [HST14] Metreleptin for treating lipodystrophy Highly specialised technologies guidance 2021. Available from: https://www.nice.org.uk/guidance/hst14.

40. NICE. Liraglutide for managing overweight and obesity Technology appraisal guidance [TA664]. 2020.

41. NICE. Naltrexone–bupropion for managing overweight and obesity. Technology appraisal guidance [TA494] 2017. Available from: https://www.nice.org.uk/guidance/ta494.

42. NICE. Rimonabant for the treatment of overweight and obese adults. Technology appraisal guidance [TA144]. 2008.

43. Alsumali A, Eguale T, Bairdain S, Samnaliev M. Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity. Obesity Surgery. 2018;28(8):2203-14.

44. Riazi A, Shakoor S, Dundas I, Eiser C, McKenzie SA. Health-related quality of life in a clinical sample of obese children and adolescents. Health and Quality of Life Outcomes. 2010;8(1):134.

45. Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D Utility Scores from the PedsQL™ Generic Core Scales. PharmacoEconomics. 2014;32(7):693-706.

46. Ara R, Blake L, Gray L, Hernández M, Crowther M, Dunkley A, et al. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review. Health Technology Assessment. 2012;16(5).

47. Argente J, Tatton-Brown K, Lehwalder D, Pfäffle R. Genetics of Growth Disorders-Which Patients Require Genetic Testing? Front Endocrinol (Lausanne). 2019;10:602-.

48. Graves LE, Khouri JM, Kristidis P, Verge CF. Proopiomelanocortin deficiency diagnosed in infancy in two boys and a review of the known cases. Journal of Paediatrics and Child Health. 2021;57(4):484-90.

49. NICE. Interim Process and Methods of the Highly Specialised Technologies Programme. Updated to reflect 2017 changes. 2017.

50. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol. 2018;6(12):944-53.

51. Søltoft F, Hammer M, Kragh N. The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Qual Life Res. 2009;18(10):1293-9.

52. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. Medical Decision Making. 2011;31(6):800-4.

53. NICE. Dapagliflozin in combination therapy for treating type 2 diabetes, Technology appraisal guidance [TA288]. . 2013.

54. NICE. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes, Technology appraisal guidance [TA390]. . 2016.

55. NICE. NICE guideline [NG49] Non-alcoholic fatty liver disease (NAFLD): assessment and management 2016. Available from: https://www.nice.org.uk/guidance/ng49.

56. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, et al. A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT. Health Technology Assessment. 2015;19(40):1-188.

57. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577-86.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

No factual inaccuracies were identified by the company during the factual accuracy check (FAC). The ERG response to the question raised by the company during the FAC is provided below.

Question 1 Modelled impact of discontinuation

Question	ERG response
Our only question is that ERG modelled the impact of discontinuation on incremental QALY and ICER. It says 1% discontinuation per year but the impact is quite high. We are unclear as to how this was implemented and why the impact is an 8% increase in ICER per Table 43. We can understand the rationale of adding a discontinuation rate given the (potentially) non-zero discontinuation rate observed in the extension studies; our contention in our response was that the discontinuation was not reported to be due to the drug, and that the impact would be in the reverse direction due to the high cost of setmelanotide administration being removed. It looks as if the impact is to move the ICER from ERG corrected company base case of GBP 166k to GBP 181k (again, Table 43). If possible, it would be good to see how this was implemented.	A treatment discontinuation of 1% every year/per cycle through the lifetime horizon of the model was implemented for responders, aligned with the clinical opinion to the ERG. The detailed assumptions made by the ERG for this scenario were highlighted in Section 6.2.2 of the report; please refer to this section for the approach. The impact of this scenario was considerable, despite the decrease in the incremental costs. This is due to the QALY loss associated with treatment discontinuation, i.e., 1% of responders discontinued every year and moved to the non-responder arm through the lifetime horizon of the model. For instance, in the case of the LEPR paediatric population, when 1% discontinuation was applied every year for the entire lifetime horizon, the incremental QALYs decreased by ~27% from [redacted] (ERG corrected company base case) to [redacted] whereas the incremental costs only decreased by ~21% from £[redacted] (ERG corrected company base case) to £[redacted]. Hence, the net impact observed was an increase in the ICER (from £166k to £181k) due to reductions in incremental QALYs being larger than the incremental cost savings resulting from the removal of setmelanotide treatment costs for discontinuing responders.