For public, no confidential information included

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome ID3947 (HST)

Lead team presentation

Chair: Peter Jackson

Lead team: Paul Arundel, Sarah Davis, Sara Payne

Evidence Review Group: Bristol TAG

Technical team: Emma Douch, Rufaro Kausi, Jasdeep Hayre

Company: Rhythm Pharmaceuticals

July 2023

NICE

Setmelanotide, Imcivree®

<table>
<tr><td>Marketing authorisation</td><td>The treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) […] in adults and children 6 years of age and above.”

Setmelanotide also has a marketing authorisation in loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency</td></tr>
<tr><td>Mechanism</td><td>Activates the MC4R neuron, which decreases appetite and increases feelings of satiety</td></tr>
<tr><td>Administration</td><td>Subcutaneous injection into abdomen at a different site; once daily</td></tr>
<tr><td>Dosage</td><td>Summary of product characteristics details daily dosing based on age:
<table>
<tr><th>Age, years</th><th>Week 1</th><th>Week 2*</th><th>Week 3 and onwards*</th></tr>
<tr><td>6 to < 16</td><td>1 mg</td><td>2 mg</td><td>3 mg</td></tr>
<tr><td>>16</td><td colspan="2">2 mg</td><td>3 mg</td></tr>
</table>
*Dose escalation subject to previous dose being well tolerated. More gradual dose titration mandated in people with renal impairment</td></tr>
<tr><td>Duration</td><td>Long-term use</td></tr>
<tr><td>List price</td><td>List price £2376 per 10mg vile
Update to confidential simple patient access scheme proposed</td></tr>
</table>

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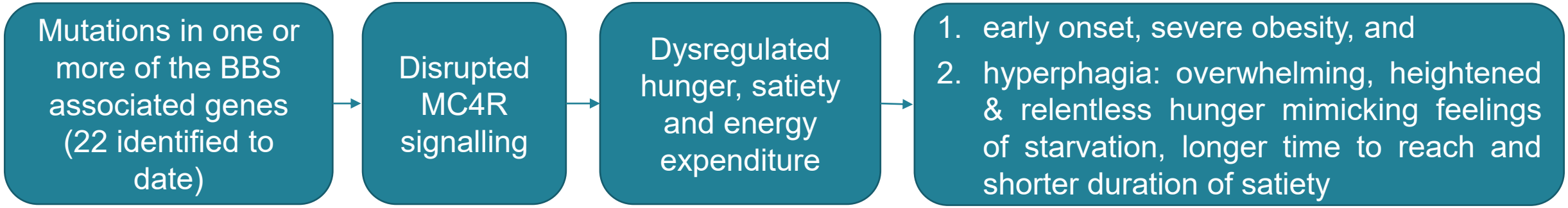
LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase 1; POMC, pro-opiomelanocortin

Key issues

Issue	Impact
Clinical effectiveness	
1. Population: a) how will BBS patients with severe hyperphagia be identified in clinical practice? b) what is the potential impact on the cost-effectiveness of setmelanotide for people with moderate hyperphagia symptoms?	 
2. Generalisability: are the results from RM-493-023 and -022 generalisable to the UK BBS population?	
3. Given the absence of other data sources, would the CRIBBS data still provide valuable information to assess the generalisability of study findings in terms of patient characteristics?	
Cost-effectiveness	
4. Treatment effect on BMI: What shift in BMI-Z class levels is most plausible for children whose disease responds to setmelanotide?	
5. Treatment effect on hyperphagia: Will all 'responders' to setmelanotide have mild hyperphagia or will some have moderate hyperphagia?	
6. BMI health state utilities: Should BMI health state utilities be calculated from literature or clinical trial?	
7. BBS utility multiplier: Should a multiplier for non-obesity-related comorbidities be applied? If yes, which source is preferred?	

Disease background: Bardet-Biedl syndrome (BBS)

Rare genetic disorders of obesity (RGDO): hypothalamic disorder affecting melanocortin-4 receptor (MC4R) neuroendocrine system



Quality of life: Associated with large QoL impact and multiple comorbidities: obesity and hyperphagia key factors affecting QoL; depression, social isolation and social stigma; vision loss can limit daily activities

Mortality: no published evidence on life expectancy: renal failure and obesity related comorbidities thought to be major causes of death

Incidence/prevalence: prevalence estimated at about 1 per 100,000 people in the UK

Company estimates 472 people in England have genetically confirmed BBS of whom 72-92% have obesity.

BBS, Bardet-Biedl syndrome, QoL, quality of life

Symptoms of BBS

Symptoms: vary by frequency and onset

Diagnosis: Relies on presence of clinical symptoms (4 primary or 3 primary features and 2 secondary features)

- Genetic testing for rare genetic obesity available in NHS

Primary and secondary diagnostic features of BBS and their frequency (Forsythe 2018)

Primary features	
Rod-cone dystrophy	93%
Extra digits	63% to 81%
Obesity	**72% to 92%**
Genital anomalies	59% to 98%
Renal anomalies	53%
Learning difficulties	61%

Secondary features	
Speech delay	54% to 81%
Developmental delay	50% to 91%
Diabetes mellitus	6% to 48%
Dental anomalies	51%
Congenital heart disease	7%
Shortening of digits	46% to 100%
Joining of digits	8% to 95%
Ataxia/poor coordination	40% to 86%
Anosmia	60%

Patient and carer submissions

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NHS England perspective

Population

- Patients have obesity and many have other symptoms including type 2 diabetes, renal failure and kidney abnormalities
- Setmelanotide may not be suitable for patients on dialysis (~5% BBS adults) and with chronic, severe renal failure (~20%)
- Split between children and adults in UK unclear

Treatment pathway

- No effective pharmacological therapy for BBS
- Usual treatment = reduced diet, exercise, behaviour change and sometimes surgery but overall ineffective partly due to habits (adherence issues) in BBS
- Treatment by specialists in Birmingham and London and GPs
- Setmelanotide could prevent/postpone the obesity-related complications (e.g. diabetes, renal impairment)
- Life-long treatment required with setmelanotide

Patient perspectives: symptoms of BBS

Submission from Bardet-Biedl Syndrome UK (BBS UK) and individual patient response

Complex disorder with multiple complications

- Hyperphagia and obesity present from babyhood
- Food seeking behaviours are extreme:
  (e.g. taking food out of bins, hoarding food for later eating)
- Obesity: affects mobility, sleep and concentration and makes exercise challenging
- Emotional and communication difficulties, anxiety, low mood and depression (exacerbated by obesity)
- Also associated with sight-loss with blindness typical by mid-teens
- Learning difficulties and chronic fatigue also common

"My child is constantly hungry and never satisfied"

"She is in constant pain, particularly around her knees and ankles. She has to use a wheelchair when out and about"

"We are extremely worried about our child's obesity and it causes constant stress and worry. We try to limit her intake of calories but find it extremely hard to manage"

Impact on carers and families

- Parents face 'endless battle' over food: must lock food cupboards and monitor children's eating
- Significantly impacts wider family, especially siblings
- Anxiety for carers about obesity, lack of mobility and strain on body

Patient perspectives: current treatments

High unmet need for specialised treatment

- Lack of understanding of BBS at local level & challenges in accessing local support for patients/carers
- No treatments for hyperphagia: BBS patients are often ineligible for other weight-loss treatments
- Specialist BBS clinics helpful but visits only every 18-24 months at 2 UK locations
- Lack of consideration for secondary symptoms (comorbidities) associated with BBS by care providers

"….local dietician support was very hit and miss and trying to get them to understand the severe hunger aspect has been very difficult"

"…doctors did not know the full effects of BBS and did not get the complexity of the condition."

Experience of setmelanotide

- Specifically targets hyperphagia allowing weight loss. This reduces stress and anxiety and improves self-esteem for patients
- May be challenging to administer via self-injection for people with:
  - Dislike or fear of needles
  - Visual impairment
- Carers have concerns: administering daily injections (potentially lifelong), side effects (e.g. skin colour changes)

"…[with setmelanotide] it was obvious I was losing weight, inches off the body, and hunger pangs had disappeared …my self-esteem and confidence had grown immensely"

Professional organisation perspectives

Submission from British Obesity and Metabolic Surgery Society (BOMSS)

Aim of treatment and current pathway

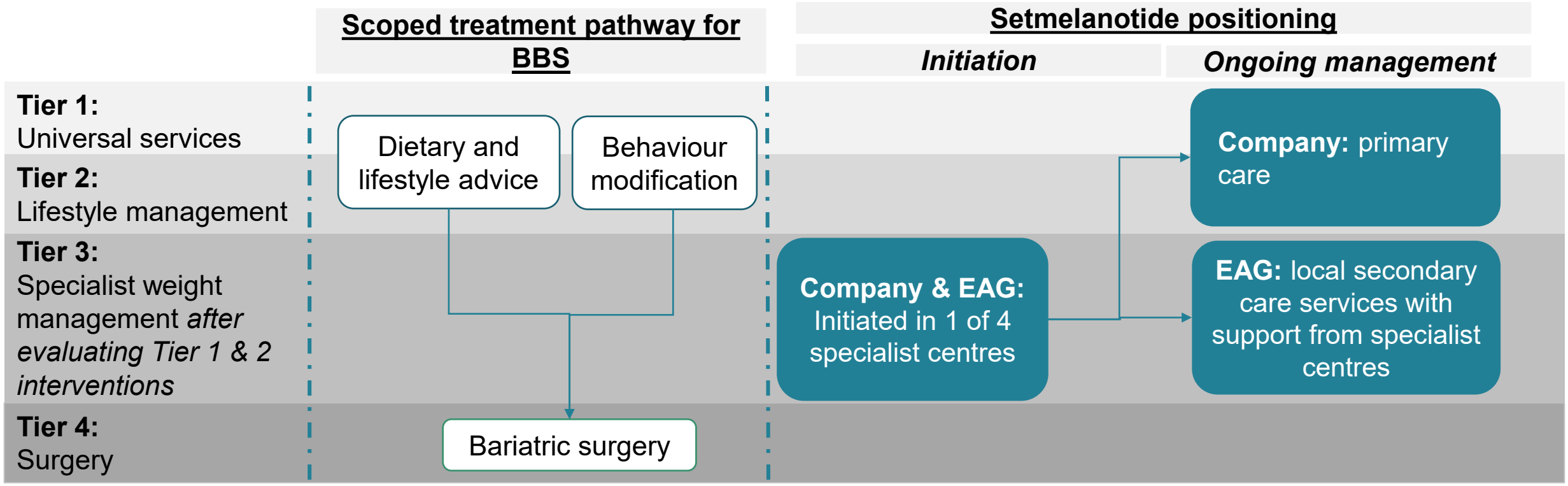
- Unmet need for effective obesity treatment options for BBS:
  - ❖ Current treatments (lifestyle intervention & occasional weight loss surgery) have variable effect
  - ❖ Population small but will benefit from novel treatment option
- Pathway well defined for all age groups and it follows current guidelines for general obesity
- Aim of treatment: weight loss maintenance improving health, function and quality of life:
  - ❖ By 10% weight loss, this is a clinically significant treatment response and likely associated with improved survival
  - ❖ Weight loss will also benefit obesity associated disease

Experience with setmelanotide

- Safe and effective in short term: major side effects uncommon in the clinical trials although there were reported side effects including skin darkening and occasional hair colour darkening

Treatment pathway

No existing guidelines or clinical pathways of care specific to BBS. Current care: according to guidelines for general obesity



- What treatment do people with BBS obesity currently have? Is bariatric surgery used in this population?
- Where are services for BBS (and ongoing monitoring) provided? Would people with BBS be referred for specialist weight management upon diagnosis or only after failure on tier 1 and 2 interventions?
- Is current positioning appropriate?

Based on Obesity: identification, assessment and management (CG189) which recommends a tier-based system.

Key Issue 1: Identifying severe hyperphagia in clinical practice

Background: Company's population (only severe hyperphagia) is narrower than the scope and MA wording

Company:

- People with severe hyperphagia benefit most from treatment
- Hyperphagia not captured in trials but underlying BBS cause
  - ❖ All trial patients had BMI ≥30 kg/m^2: suggests severe hyperphagia
  - ❖ Hunger score not reliable measure in BBS & no validated measurement scale for hyperphagia
- Experts: 60% BBS children have severe hyperphagia in clinical practice (as per company definition): expect similar for adults
- Patients treated at BBS specialist centres by experienced clinicians. Will identify severe hyperphagia as patients who:

1. report continuous hunger, despite recent food intake
2. overeat at meals & eat constantly, including at night
3. show distress/ inappropriate behavioural response if denied food
4. have rapid or continued weight gain despite diet & exercise
5. eating habits hard for caregivers to manage (hide/ration food)

EAG: No clinical assessment tool to measure hyperphagia in trials: no direct evidence of impact of setmelanotide on hyperphagia

- Unclear how severe hyperphagia identified in clinical practice
  - ❖ Likely based on BMI/BMI-Z & clinical impression
  - ❖ Population may be broader than company defines
- Company's symptom assessment makes N with severe hyperphagia correctly identified in practice uncertain
- Explore impact on ICER of including people with moderate hyperphagia

BMI, body mass index, ICER, incremental cost-effectiveness ratio; N, number

Clinical experts: Clinical history & scores aids diagnosis of severe hyperphagia

- How will severe hyperphagia be identified in clinical practice?
- Is the company's population appropriate?

Clinical effectiveness evidence

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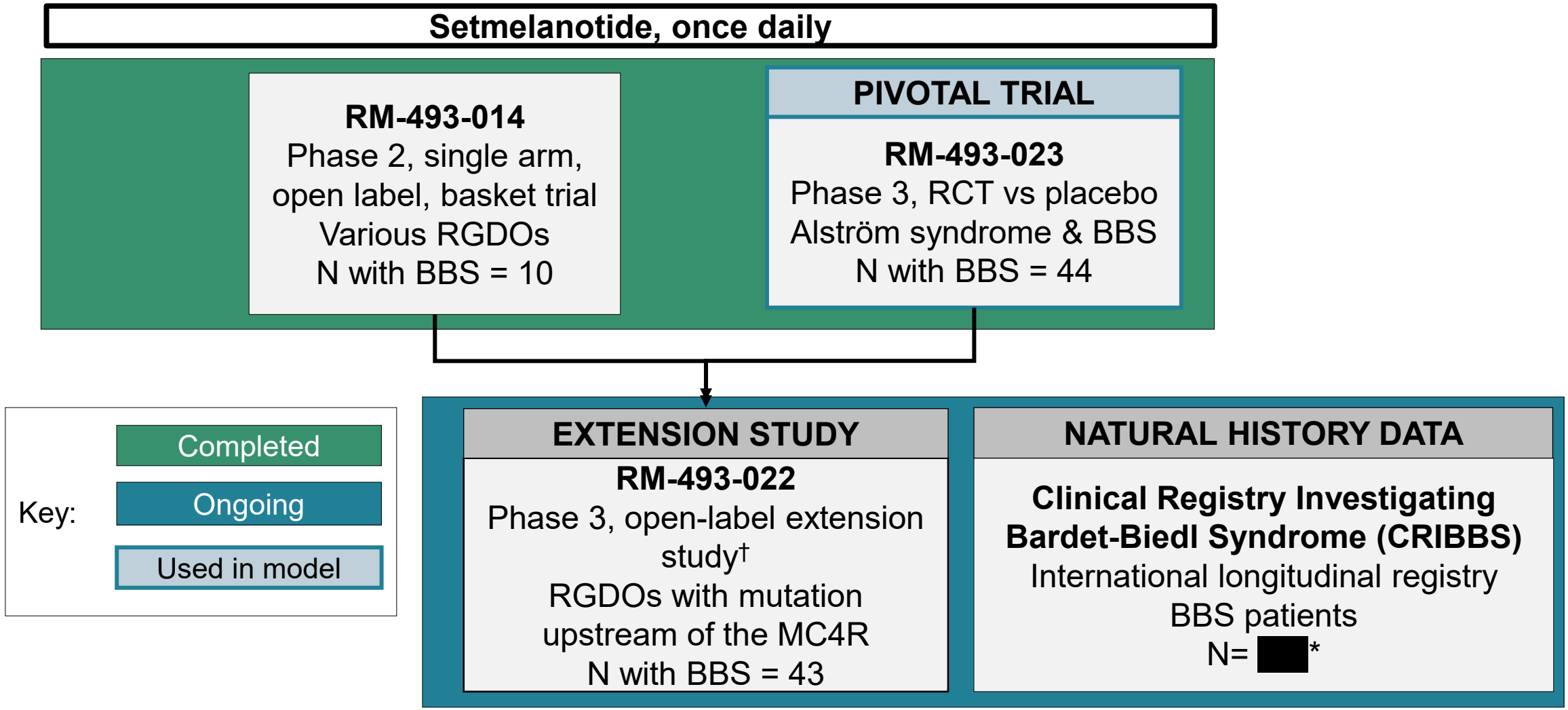
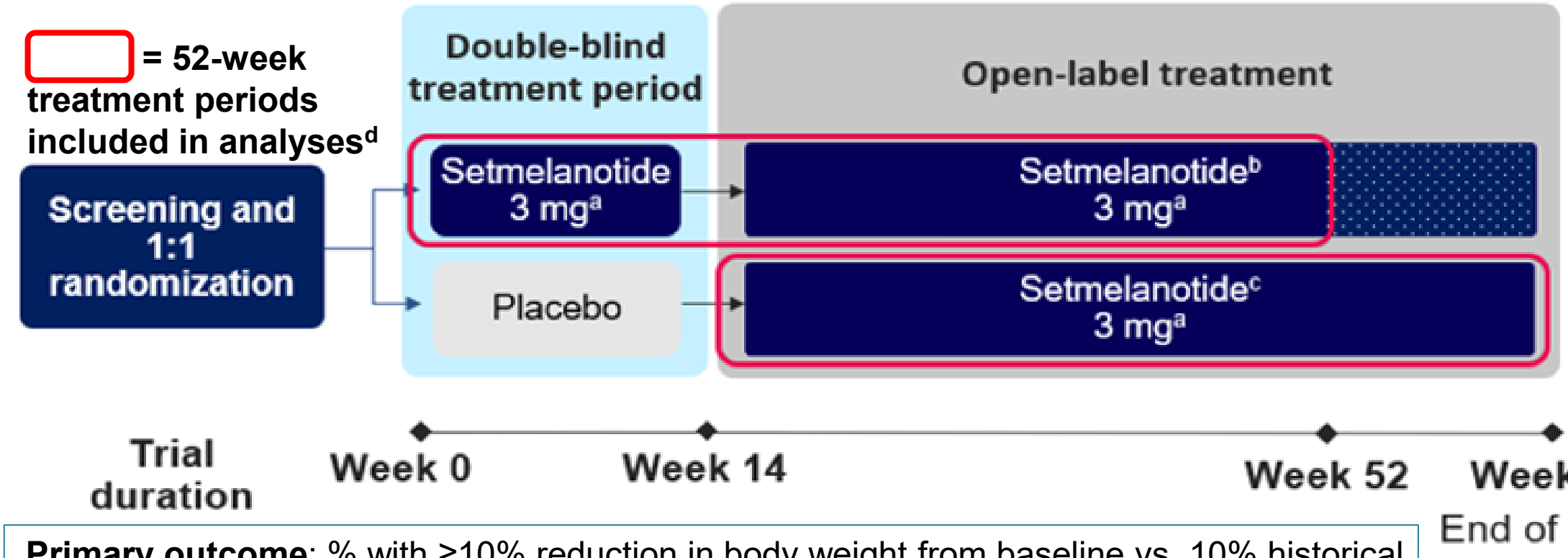
Overview of clinical trials



† Study ongoing but no new data output anticipated for BBS patients *Only people with BBS aged > 12 years used in analyses to limit the effect of growth and development on detection of weight loss

N, number; RCT, randomised controlled trial; RGDO, rare genetic disorders of obesity

RM-493-023, company's pivotal trial: study schema



Primary outcome: % with ≥10% reduction in body weight from baseline vs. 10% historical control rate from the CRIBBS registry

[a] Dose escalation up to 3.0 mg based on age

[b] For patients who received ≥52 weeks of setmelanotide by end of study, analysis performed at Week 52.

[c] A multiple imputation model was used to impute data for patients who received <52 weeks of setmelanotide at the 1° analysis timepoint

[d] Efficacy outcomes assessed at 52 weeks of active treatment for each group (Week 0 - 52 for setmelanotide; Week 14 - 66 for placebo)

RM-493-022
Open-label extension study (OLE)

- Further 2 years at therapeutic dose
- Assessment every 3 months until end of study
- No specific guidance on diet / exercise provided during trial

Source: company submission, Figure 3

Key issue 2: Generalisability of trial populations to the NHS (1)

Background: Company's studies are small, with limited UK patients, meaning the similarity between the UK population and trial population is unclear

Characteristic	RM-493-023		RM-493-022
	Setmelanotide (N=22)	Placebo (N=22)	Setmelanotide (N=42)
Age (Mean, SD)	19 (10)	22 (13)	[redacted]
Sex (Female %)	41	68	[redacted]
Race (%)			
White	68	86	[redacted]
Black or African American	5	5	[redacted]
Asian	0	5	[redacted]
Other	27	5	[redacted]
Weight, kg (Mean, SD)	110 (36)	107 (32)	Index Study+: [redacted] Extension Study^: [redacted]
BMI, kg/m² (Mean, SD)	41 (10)	42 (10)	Index Study+: [redacted] Extension Study^: [redacted]
Most/worst hunger (Mean, SD)	4.7 (1.6)	6.8 (2.0)	NR

+ baseline value from 'index' study to which patient originally recruited (RM-493-023 or RM-493-014) before joining extension study

^ baseline value as measured on recruitment to extension study RM-493-022.

BMI, body mass index; GLP,-1 Glucagon-like peptide-1, N, number; NR, not reported; SD, standard deviation

Key issue 2: Generalisability of trial populations to the NHS (2)

EAG*:*

- Baseline BMI similar to UK population but **only 2 UK patients**: lack of generalisability to NHS population?
- Some discrepancies in baseline characteristics in key subgroups:
  1. **Follow up in RM-493-023:** ≥52 week follow up = slightly higher [redacted] than < 52 weeks
  2. **Pivotal v supplemental cohort in RM-493-023:**
     - ❖ BMI and mean age balanced.
     - ❖ Supplemental cohort = lower mean weight and % white, non-Hispanic, and non-Latin participants
- Baseline characteristics not provided stratified by:
  1. **Hyperphagia severity:** not assessed qualitatively or quantitatively in trials: validity to decision problem?
  2. **Index trial for extension study (RM-493-014 / -023):** unclear if baseline doses comparable across studies

Prefer*:* use of CRIBBS database to characterise UK based BBS patient population & compare with trial population

Company (response to TE): Clinical expert advice: baseline characteristics similar to UK population (77-86% white in trials comparable to 82% in UK ONS data)

- Too few UK patients in CRIBBS registry to characterise UK BBS population (N [redacted] of which subset have longitudinal data on weight gain)

Clinical experts: Clinical setting and treated population in trial likely similar to those in UK

- Are studies RM-493-023 and RM-493-022 generalisable to NHS practice?
- Given the absence of other data sources, would CRIBBS data still provide valuable information to assess the generalisability of study findings in terms of patient characteristics?

BMI, body mass index; CRIBBS, Clinical Registry Investigating Bardet Biedl Syndrome; GLP,-1 Glucagon-like peptide-1; N, number, ONS, office for National Statistics, TE, technical engagement

Clinical effectiveness results

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Clinical trial results: weight loss

RM-493-023

14-week RCT results, all BBS patients, PCAS			
Result	**Setmelanotide (n=10)**	**Placebo (n=12)**	**Difference (95% CI)**
Mean % change in body weight in patients aged ≥12 years (SD)	[redacted]	[redacted]	[redacted]

52-week single-arm setmelanotide results, pivotal patients, FAS	
Result	**Setmelanotide**
Mean % change in body weight from baseline in patients aged ≥12 years, kg (%) (n=15)	-9.42 (-7.57%)
% with ≥10% reduction in body weight from baseline, % (95% CI) p-value (vs. 10% historical control rate)	
≥12 years old **(1º outcome)** (n=28)	[redacted]
≥18 years old (n=15)	46.7 (21, 73), p= 0.0003

RM-493-022 (OLE)

OLE results suggest sustained weight loss from index study baseline but few patients (N=[redacted]) with results at 36 months:

- Mean % weight reduction from baseline: [redacted]% at month 12, [redacted]% at months 16 and 24, [redacted]% at month 36
- % patients maintaining ≥10% weight reduction from index trial baseline: [redacted]% at month 12, [redacted]% at month 18, [redacted]% at month 24, [redacted]% at month 36.

- What is the committee's view on: a) setmelanotide's treatment effect on weight loss? b) whether this treatment effect is sustained?

Red = result used in company model. 1º , primary; FAS, full analysis set; OLE, open label extension study; PCAS, Placebo-controlled analysis set; SD, standard deviation

Clinical trial results: BMI

[redacted]

BMI, body mass index; FAS, full analysis set; OLE, open label extension; PCAS, Placebo-controlled analysis set.

RM-493-023

- Difference in mean BMI Δ between setmelanotide (n=22) and placebo (n=22) at week 14 (RCT, all BBS patients, PCAS): [redacted]% (95% CI [redacted]%, [redacted]%), p= [redacted]

For children, company considers BMI Z-score more appropriate than body weight to characterise obesity

- **85.7**% had ≥0.2-point reduction in BMI-Z score at week 52 (pivotal patients, FAS, n=14)

Post-hoc analyses of most common BMI class shift in 'responders' (PCAS):

- [redacted] adults had a [redacted] class level shift in BMI
- [redacted] children had a [redacted] class level shift in BMI-Z

RM-493-022 (OLE)

- Mean % BMI from baseline (all age groups): [redacted]% at month 12 (n=[redacted]) maintained to [redacted]% at month 36 (n=[redacted])
- % children maintaining ≥0.3 BMI-Z score reduction from index trial baseline: [redacted]% at month 18 (n=[redacted]), [redacted]% at month 24 (n=[redacted]), [redacted]% at month 36 (n=[redacted])

- What is the committee's view on setmelanotide's treatment effect on BMI?
- Does evidence suggest it is effective in reducing BMI in the long term?

Red = result used in company model.

RM-493-023, 52-week results, hunger and QoL

Hunger, pivotal patients aged ≥12 years without cognitive impairment, FAS	
Mean change in weekly average daily hunger score, % (SD, n=14)	
average over 24 hours	[redacted]
most/worst over 24 hours	-30.5 (26), p0.0004
morning hunger	[redacted] p0.0024
% with ≥25% daily hunger score reduction (n=14)	57.1, p<0.0001
Quality of life, pivotal patients without cognitive impairment, FAS	
Mean change in IQWOL-Lite, patients ≥18 years (n=11)	+12
Mean change in PedsQL, patients ≥18 years (n= 3)	+3.3
EQ-5D-5L, mean change in VAS, patients ≥16 years (n=13)	[redacted]

EAG:

- Greater reductions in weekly average of daily hunger score also observed for setmelanotide vs placebo at 14 weekS
- No HRQoL results for carers or BBS patients from 14-week RCT
- SF-36 and SF-10 health survey for children collected in RM-493-023 and -022: not reported and unclear if QoL measure validated for BBS population

Hunger and quality of life not measured in RM-023-022 (OLE) so no analyses past week 52 available

- What is the committee's view on a) setmelanotide's treatment effect on hunger and quality of life? b) the lack of evidence on carer quality of life?

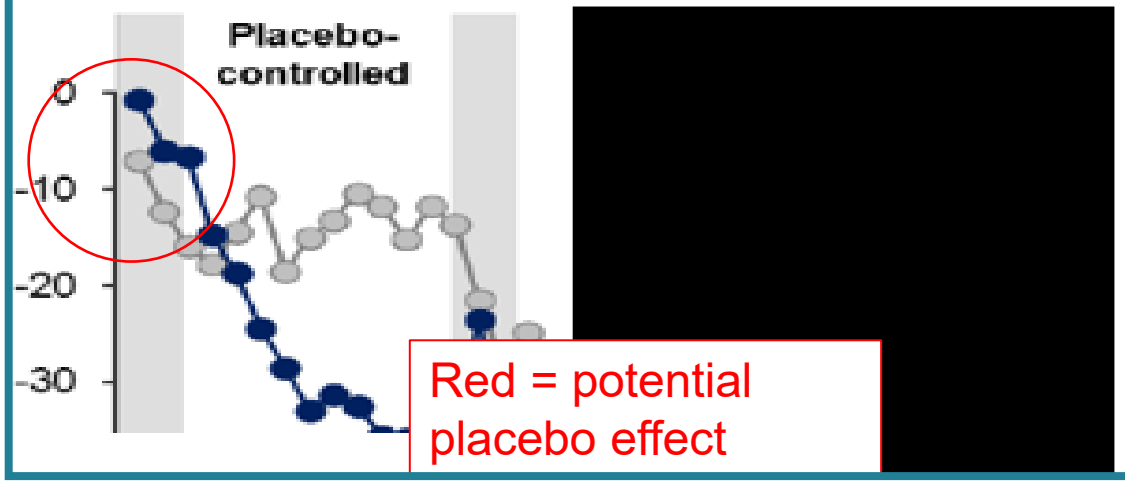
FAS, Full analysis set; HRQoL, health related quality of life; OLE, open label extension; SD, standard deviation; RCT, randomised controlled trial; VAS, visual analogue scale
IQWOL-Lite: A change of 7.7 to 12 points (dependant on baseline score) demonstrates clinically-meaningful improvement.

Key issue 4: Potential bias from lack of RCT at 52 weeks

Background: Outcomes at week 52 are from the single arm extension period of RM-493-023
Potential placebo effect/ regression to mean observed during titration and re-titration periods for hunger and BMI

Mean change in a) max hunger score and b) BMI (%)

a) b)



Clinical experts: Would not expect weight & hunger fluctuations over time in people having BSC

EAG: Placebo effect/ regression to mean important: could be ~10% treatment effect

- No control group at 52 weeks: observed effect may not be setmelanotide alone
- Larger treatment effect in setmelanotide group = regression to the mean + treatment effect.
- Difference between week 14 and 24 in placebo group only = treatment effect adjusting for regression to mean:
  - ❖ Still substantial effect but smaller than for those randomised to setmelanotide

Company:

- BBS rare disease: traditional RCTs challenging
- Placebo effect negligible & constant to week-52 -> not regression to the mean
- Hunger scores, BMI/ BMI-Z & weight virtually unchanged in placebo patients during RCT. No adjustment needed.
- Semaglutide studies: placebo response plateaus ~week 16

- What is the impact of potential bias from lack of RCT comparisons at 52 weeks in RM-493-023?
- Should results be adjusted for placebo effect/regression to the mean?

BMI, body mass index, RCT, randomised controlled trial

Summary of results used in the economic model

Post hoc analyses by age (adult & children) used in the model

	Adults	Children	Application in model
Directly inform the model			
Post hoc outcomes (FAS)	**N=15**	**N=14**	
Proportion of patients achieving ≥10% reduction in weight from baseline to 52 weeks	46.7%	Not used in model: inappropriate for growing children	**Response rates to setmelanotide: put into model as 14-week data**
Proportion of children achieving a BMI Z score reduction of ≥0.2 from baseline to 52 weeks	NA	85.7%	
Post-hoc outcomes (PCAS)	[redacted]	[redacted]	
Most common reduction in BMI class from baseline to 52 weeks	[redacted] BMI class	[redacted] BMI class	**Treatment effect on BMI**

- How reliable and valid are the clinical effectiveness results used in the modelling?
- Is it appropriate to use response at 52 weeks to inform response at 14 weeks?

BMI, body mass index; FAS, full analysis set; N, number; PCAS, placebo-controlled analysis set

Cost effectiveness evidence

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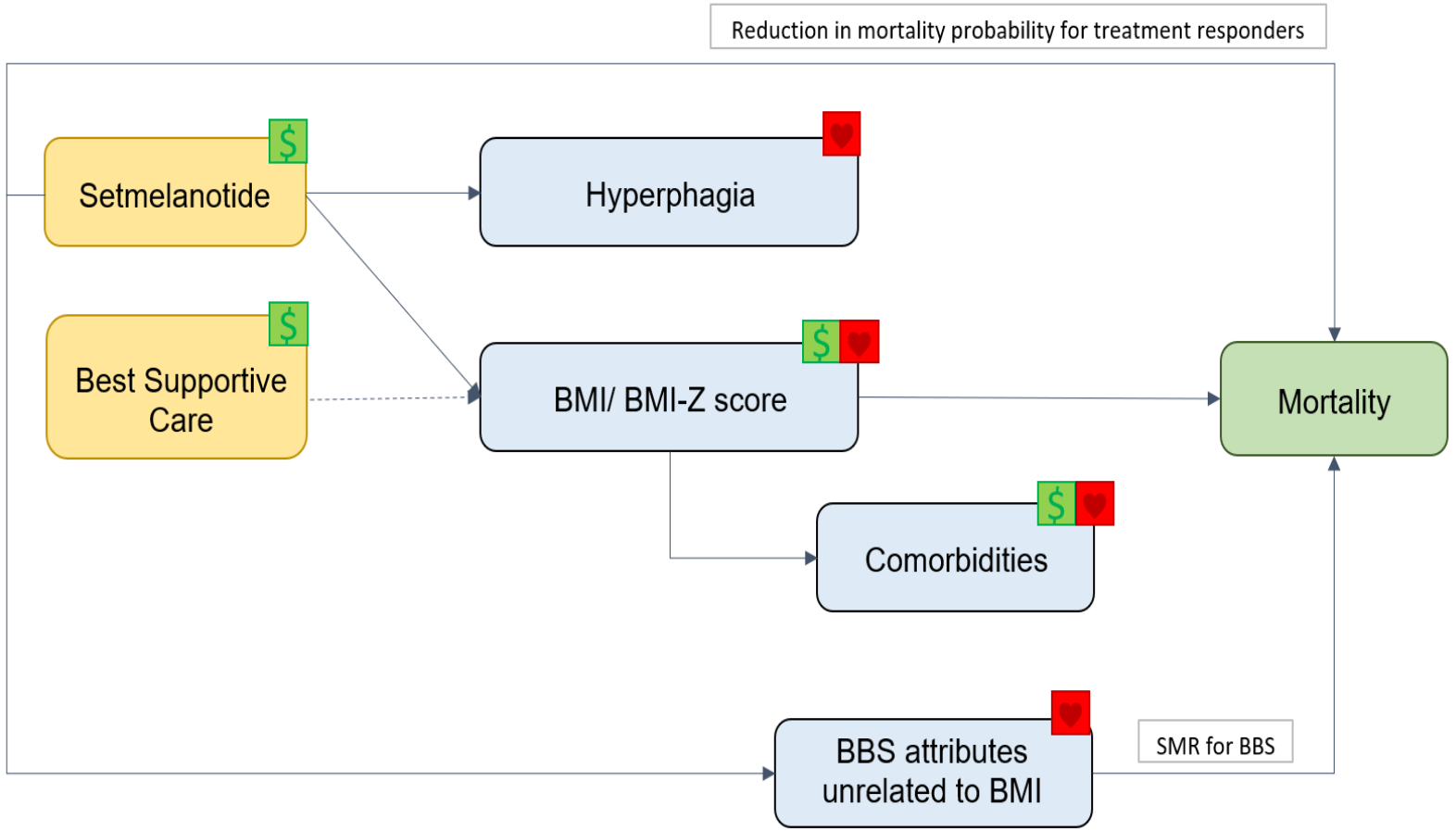
Model structure

How costs and QALYs accrue in the company's model



Cost

Quality of life (patient/caregiver)

- Lifetime model based on UK life table with BMI score (adults) or BMI-Z score (children) health states
- BSC: patients stay in same BMI state throughout lifetime
- Setmelanotide: patients change BMI/BMI-Z class based on response: applied at 14 weeks
  - ❖ Non responders revert to baseline BMI and hyperphagia status
- Small proportion stop setmelanotide each year and return to baseline BMI/BMI-Z health state
- At age 18, patients BMI-Z score is mapped to the relevant BMI health state

BSC, best supportive care; BMI, body mass index; QALY, quality adjusted life year

Evidence sources and assumptions

Evidence/ Assumptions	Company
Model structure	Lifetime model based on UK life table with BMI/ BMI-Z score-based health states
Intervention	Setmelanotide + BSC: lifestyle and dietary interventions and behavioural therapy
Comparator	BSC alone
Response	RM-493-023 for: • % responders at 14 weeks (assessed at 52 weeks in trial)* • Decrease in BMI/BMI-Z-score class for responders 100% of responders transition to mild hyperphagia at 14 weeks BSC: no change from baseline
Dosing	Day 1 + dose titration: average starting dose & predicted titration dose from clinical trial Post-titration dose: expected dose for real-world population
Baseline characteristics	Baseline BMI/BMI-Z score and gender: RM-493-023 Hyperphagia distribution: assumed all patients have severe hyperphagia (expert opinion)

BSC, best supportive care; BMI, body mass index. *Responders defined as ≥10% weight loss in adults or ≥.2 reduction in BMI Z-score in children

Evidence sources and assumptions

Evidence/ Assumptions	Company
Model starting age	6 years old **Subgroup analyses**: all patients enter the model as adults, split between adults & children as per clinical practice
Time horizon	Lifetime
Discontinuation	1% annually: return to baseline BMI/BMI-Z class and hyperphagia status
Mortality	Using Standardised Mortality Rate (SMR) by BMI-Z / BMI class Further SMR for BBS patients vs. general population. No mortality benefit assumed for setmelanotide over BSC

EAG: Lifetable cohort model appropriate for modelling mortality and co-morbidities as functions of age and BMI/BMI-Z. However, very strong assumptions were made that are unlikely to hold:

- Patients stay in the same BMI states for the rest of their lives unless they discontinue treatment.
- All patients move to and stay in mild hyperphagia state whilst on treatment, and this is unrelated to change in BMI/BMI-Z.

- What is the committee's view on the company's model structure?

BSC, best supportive care; BMI, body mass index

Modelling treatment effect

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Key issue 6: Modelling hyperphagia

Background: company assumes 100% have severe hyperphagia at baseline and all responders move to mild hyperphagia at week 14

EAG:

1. Baseline status: Setmelanotide may be used in some people with moderate hyperphagia

- **Scenario:** 60% severe, 40% moderate hyperphagia at baseline (expert option: 60% children have severe hyperphagia in practice)

2. Treatment effect: over-simplification: some responders likely have moderate hyperphagia

- variability in % Δ in most/worst hunger in RM-493-023 adults
- BMI-Z Δ varies: suggests spread of effects
- Hyperphagia modelled independently to BMI:
  - Expect bigger hyperphagia response = bigger BMI-Z / BMI response
  - Absence of direct trial data: have to infer effect on hyperphagia from effect on BMI
- **Base case:** [redacted]% move to mild and [redacted]% to moderate (% moving 2 & 1 BMI-Z class in trial)

Company: 1. Baseline status: aligned with updated decision problem (severe hyperphagia only)

2. Treatment effect: EAGs approach inappropriate:

- 'responders' needed sustained Δ in BMI-Z (and eating habits) over 1 year: only possible with mild hyperphagia
  - ❖ [redacted] class BMI reduction indicates slower change in eating habits not moderate hyperphagia
- BMI not reliable proxy for hyperphagia: hunger, eating habits, sleep, mood, personal relationships uncaptured
- Experts: support all responders moving to mild hyperphagia
- Approach conservative: no one moves to "no hyperphagia"
- Multifactorial correlation between hunger and hyperphagia: cannot use hunger scores as proxy

Clinical experts: Small population: hard to define % with severe hyperphagia in practice but may be ~50-60%

- Correlation with BMI and hyperphagia but controlling hyperphagia improves QoL independent of weight loss
- Cognitive abilities in adults and parental resources in children also affect outcomes

- Which assumptions are most plausible to model the effect of setmelanotide on hyperphagia?

BMI, body mass index; TE, technical engagement

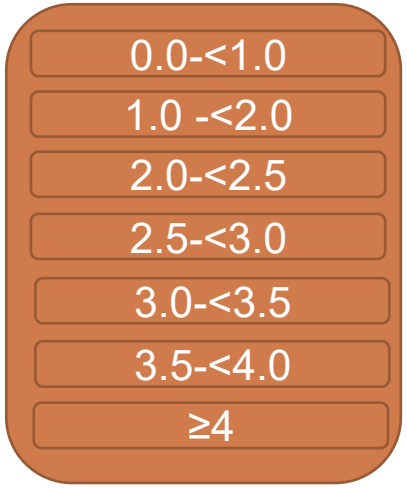
Key issue 7: initial treatment effect on BMI

Background: company modelled treatment effect by applying observed BMI reduction at week 52 in RM-493-023:

Post hoc analyses of most common change in BMI class levels were:

- children: [redacted] BMI-Z class
- adults: [redacted] BMI class

BMI-Z score health states in the model



Higher BMI-Z = more severe obesity.

EAG: BMI-Z class changes uncertain: [redacted] class level drop may overestimate effect.

- Forsythe et al 2021 reported results after 1 year of treatment in RM-493-023: mean Δ in BMI-Z (n=9) of -0.7 (= [redacted] class Δ)
- [redacted]
- Small number in analyses, no control arm
- Acknowledge true effect between a [redacted] & [redacted] class drop: company doesn't account for regression to the mean in placebo group

Alternative approach: apply mean BMI-Z Δ from trial to continuous distribution of baseline BMI

Base case: [redacted] level BMI-Z class drop for children

Company: BMI Z-scores more appropriate way to characterise obesity in children than change in body weight

[redacted] class BMI-Z drop in children justified:

1. Larger intervals at extremities with intervals of 0.5 BMI-Z score for BMI-Z classes between 2-4
   - If classes at the extremities had a range of 0.5 BMI-Z score (n=12):
     - ❖ Mean shift is [redacted] BMI-Z score classes
     - ❖ Mean difference in BMI-Z score = [redacted] (or a [redacted] class change with a 0.5 BMI-Z score interval)
2. Expect greater benefits in clinical practice when exercise & dietary modifications allowed

- What shift in BMI-Z class levels is most plausible for children?

BMI, body mass index

Key issue 8: Long term treatment effect

Background: After initial response, patients stay in same BMI/BMI-Z class whilst on treatment (no effect waning)

- Company models an annual 1% stopping rate in 'responders' as proxy for treatment waning

Company: 1% annual discontinuation rate in model:

- Accounts for gradual waning not leading to immediate discontinuation
- Used in NICE HST21 to capture burden of constant injections/AEs (especially skin pigmentation)

Base case conservative:

- ❖ Doesn't consider ↑ in BMI/BMI-Z for people having BSC: setmelanotide stops increasing weight trajectory
- ❖ People who discontinue revert back to baseline BMI-Z and hyperphagia state (no tapering of effect): eating habits and BMI effect would be maintained

- Clinical experts: no waning of effect on hyperphagia -> restores lost MC4R pathway signalling (on/off response)
- People will discontinue early if due to lack of efficacy/ AEs: shouldn't count towards yearly discontinuation rate

EAG: No long-term evidence to inform treatment effect.

- Clinical advisors expect some waning of effect:
  - ❖ GLP-1 receptor agonists: small waning of effect at 104 weeks
- Including stopping rate appropriate but company may underestimate true value:
  - ❖ Doesn't capture people with reduced benefit who stay on treatment (& incur costs)
  - ❖ RM-493-023: [redacted] ([redacted]%) stopped treatment for AEs and [redacted] ([redacted]%) for lack of efficacy: long-term stopping rate may be >1%

Base case: 2% annual discontinuation rate
Scenario: 1% waning of treatment effect

Clinical experts: Most obesity interventions show fatigue over time.

- What is the committee's view on the modelling of setmelantide's treatment effect in the long-term?

AE, adverse event; BSC, best supportive care; BMI, body mass index, GLP,1 glucagon like peptide 1; HST, highly specialised technology

Health-related quality of life

NICE

Summary of utilities in the company model

Description	Utility	Source
Health state utilities		
BMI z-score utility (children)	Separate utilities by BMI-Z score. Range from 0.89 (BMI-Z 0-1) to 0.81 (BMI-Z ≥4.0)	• General obesity PedsQL (Riazi et al. 2010) mapped to EQ-5D for BMI-Z scores 0.0 -1.0 and 3.5 – 4.0. • Other BMI-Z utilities extrapolated
BMI score utility (adults)	Separate utilities by BMI score and age ranging from 0.91 (BMI 20-25, 18 – 30 years old) to 0.66 (BMI ≥50, >70 years old)	US SF-12 study for morbid obesity (Alsumali et al. 2018), mapped to EQ-5D
Hyperphagia multiplier		
Mild	0.909	Company vignette study, with all negative utilities set to 0.
Moderate	0.702	
Severe	[redacted]	
Other utility multipliers/decrements in the model		
BBS multiplier	0.8	Company assumption
AE disutility	• Nausea/ vomiting: -0.04 ([redacted]% patients) • Injection site erythema: -0.011 ([redacted]% patients)	Matza et al, applied at 14 weeks
Comorbidities	Various	Various, as per HST21
Carer disutility	0.0986	As per HST21 and HST14. Applied to both BSC and setmelanotide arms.

BMI, body mass index; HST, highly specialised technology; PAS, patient access scheme

Key issue 9: source of health-state utilities (1)

Background: EQ-5D, PedsQL & IWQOL-Lite collected in RM-493-023 but not in base case:

- Company deemed not sensitive enough to capture effect of hyperphagia on QoL and instead use:
  - ❖ literature based utilities in general obesity for BMI
  - ❖ vignette study utilities from HST21 for hyperphagia
- Company provided a scenario at technical engagement mapping PedsQL data from RM-493-023 to EQ-5D on the EAG request
- Functional health in RM-493-023 & -022 captured using SF-36 and SF-10: not reported in company submission

EAG: Agree EQ-5D may lack sensitivity to capture QoL improvement from ↓ hyperphagia

- Forsythe et al (2023) reported PedsQL (n=9 children) and IWQOL (n=11 adults) from RM-493-023: more reliable source as BBS specific

Issues with company's mapping of PedsQL data:

1. Company incorrectly applied Khan (2014) algorithm (to patient means per BMI class not individual data)
   - Unclear if incorrect mapping approach also used for base case scores from Riazi et al.
2. Company only considered 9 patients for analyses: unclear if these were the only ones with baseline PedQL data:
   - Of these, 4/9 patients used in the mapping due to split over BMI classes: others extrapolated -> may not be representative of clinical practice

Base case: corrected EQ-5D values mapped from PedsQL trial scores (acknowledging uncertain approach)

- ❖ Avoids use of BBS multiplier as already captured in trial utilities

BMI, body mass index; HST, highly specialised technology; IQWOL, Impact of Weight on Quality of Life; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; SF, Short Form

Key issue 9: source of health-state utilities (2)

Company (response to TE): PedsQL data mapped to EQ-5D inappropriate for post-treatment utilities because:

1. Lacks sensitivity to capture hyperphagia impact on QoL
2. Existing questionnaires inappropriate where patients adapted to living with condition (e.g. hyperphagia).
3. Mapping PedsQL to EQ-5D doesn't improve uncertainty as neither questionnaires include domains that sufficiently capture impact of hyperphagia:
   - "*How I Get Along with Others*" likely obesity-related not hyperphagia-specific impacts
4. Limited PedsQL data available at week 52 for mapping (N=3 patients without cognitive impairment)

Sources of utility by BMI-Z score

BMI Z-score	Company base case (& HST21)		Company's mapping, PedsQL to EQ-5D		EAG's mapping, PedsQL to EQ-5D	
	Utility	Source	Utility	Source	Utility	Source
0.0-1.0	0.94	Riazi et al. 2010	0.94	Riazi et al. 2010	[redacted]	1 patients' baseline PedsQL score in RM-493-023
1.0-2.0	0.92	Extrapolated	0.91	Extrapolated	[redacted]	Extrapolated
2.0-2.5	0.89	Extrapolated	0.89	Extrapolated	[redacted]	Extrapolated
2.5-3.0	0.87	Extrapolated	0.86	Extrapolated	[redacted]	Extrapolated
3.0-3.5	0.84	Extrapolated	0.84	Extrapolated	[redacted]	Extrapolated
3.5-4.0	0.82	Riazi et al. 2010	0.81	Extrapolated	[redacted]	Extrapolated
≥4.0	0.80	Extrapolated	[redacted]	4 patients' baseline PedsQL score in RM-493-023	[redacted]	4 patients' baseline PedsQL score in RM-493-023

- Which approach to calculating utility values is preferred for BBS?

N, number; HST, highly specialised technology; QoL, quality of life, TE, technical engagement

Key issue 10: utility multiplier for the BBS population

Background:

- Company applies multiplier of 0.8 to all patients to capture the impact of non-obesity-related co-morbidities for BBS patients
- At technical engagement it submitted a scenario using PedsQL data from trial baseline to calculate a multiplier for BBS

Company & EAG's BBS multipliers derived from PedsQL baseline scores, RM-493-023

BMI Z-score	Riazi et al. 2010	Company		EAG	
		Baseline PedsQL scores, RM-493-023 mapped to EQ-5D	Difference (BBS utility multiplier)	Baseline PedsQL scores, RM-493-023 mapped to EQ-5D	Difference (BBS utility multiplier)
3.5-4.0	0.82	-	[redacted]	-	[redacted]
≥4.0	-	[redacted]		[redacted]	

EAG comments:

- Company introduces 'ceiling effect' for BBS patients: appropriate with considerable burden of non-obesity related co-morbidities
- But 0.8 multiplier based on company assumption **not clinical evidence**
- Large impact on ICER
- Company's scenario uncertain: based on Riazi et al. 2010 which may be incorrectly mapped

Base case: no BBS multiplier (non-obesity related comorbidities captured in PedsQL based BMI health state utilities)

Scenarios: Utility multipliers of 0.7, 0.9 and [redacted]

Clinical experts: Weight loss maintenance in BBS likely to reduce risk of type 2 diabetes, cardiovascular disease cancer: ultimately increase life expectancy

Patient experts: sight loss leading to blindness in mid-teens common in BBS.

BMI, body mass index; HRQoL, health-related quality of life, ICER, incremental cost effectiveness ratio

- Which utility multiplier best captures the impact of non-obesity related co-morbidities?

Key issue 11: Number of carers in the model

Background: Company base case after TE applies a disutility for carers based on an average 1.5 carers for children, [redacted] carers for adults. Limited clinical information to inform the level of care for BBS patients.

Company

- Experts: most patients have caregivers (adults and children), often because of cognitive impairment
- Carers greatly impacted by patients' hyperphagia: report depression, anxiety and marriage break up
- BBS UK data (N=121 adults, not provided) shows average of [redacted] caregivers

EAG: Appropriate to include carer disutilities: high impact of BBS on HRQoL of family

- Carer disutility high: -ve QALYs accrue within 11 years
- Experts state:
  - ❖ Carers have less control of diet & lifestyle as adults: most care for non-obesity related conditions (eye problems, cognitive impairment)
  - ❖ Number of carers for adults varies (range 0-20)

Base case: [redacted] carers for adults as per BBS UK data (although data not provided for verification)

Clinical experts: Usually 1-2 carer per adult patient

NB. Carer disutility applied in HST 21 at an equal rates for adults and children

- How many carers would adult BBS patients require?

HRQoL, health-related quality of life; N, number; QALY, quality adjusted life year, TE, technical engagement

Cost effectiveness results

Differing assumptions in company & EAG base cases

Assumption	Company base case	EAG base case	Impact
Treatment effect on hyperphagia	100% of responders move from severe to mild hyperphagia	Responders move to moderate ([redacted]%) or mild ([redacted]%) hyperphagia based on proportion with a BMI-Z 1 or 2 class drop respectively.	
Treatment effect on BMI-Z in children	[redacted]-level BMI-Z class drop	[redacted]-level BMI-Z class drop	
Discontinuation rate	1% (as per HST21)	2% (as per company's study)	
Health state utilities	Derived from Riazi et al.	Mapped from RM-493-023 PedsQL scores	
BBS multiplier	0.8	Not included	
Monitoring visits	Primary care	Secondary care weight-management clinics	

 Large impact: >£10,000 per QALYS gain change from base case;
 Moderate impact: <10,000 per QALY gained change from base case

BMI, body mass index; HST, highly specialised technology, QALY, quality adjusted life year

Company probabilistic base case (Paediatric, Adult and Mixed Population results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER†
Company base case (paediatric population)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,641
Adult population							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,614
Mixed population (60% paediatric and 40% adult)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£204,894

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG probabilistic base case (Paediatric, Adult and Mixed Population results)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER†
EAG base case (paediatric population)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£203,784
Adult population							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222,857
Mixed population (60% paediatric and 40% adult)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,457

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG cumulative base case (paediatric population)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER†
Company's updated base-case							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,641
+ 2% discontinuation rate (assumption 1)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£195,611
+[redacted]% of patients moving to mild hyperphagia, and [redacted]% to moderate (assumptions 1 + 2)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£219,365
+children who respond to treatment have [redacted]-level reduction in BMI-Z / BMI class (assumptions 1 + 2 + 3)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£235,157
+ updated physician monitoring visit costs and an additional visit in years 2+ (assumptions 1 + 2 + 3 + 4)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£235,857
+ Corrected mapping of PedsQL to BMI health states (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£203,784

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG cumulative base case (mixed population: 60% paediatric, 40% adult)

Interventions	Total Costs	Total undiscounted QALYs	Total QALYs	Incremental Costs	Incremental undiscounted QALYs	Incremental QALYs	ICER†
Company's updated base-case							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£204,894
+ 2% discontinuation rate (assumption 1)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£203,589
+[redacted]% of patients moving to mild hyperphagia, and [redacted]% to moderate (assumptions 1 + 2)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£229,242
+children who respond to treatment have [redacted]-level reduction in BMI-Z / BMI class (assumptions 1 + 2 + 3)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,532
+ updated physician monitoring visit costs and an additional visit in years 2+ (assumptions 1 + 2 + 3 + 4)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,309
+ Corrected mapping of PedsQL to BMI health states (assumptions 1 + 2 + 3 + 4 + 5)							
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
setmelanotide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,457

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported. BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG scenario analyses

No.	Scenario	Paediatrics			Mixed (60% paediatric, 40% adult)		
		Incremental undiscounted QALYs	ICER†	Δ from base case	Incremental undiscounted QALYs	ICER†	Δ from base case
0	Company's updated base case (probabilistic)	[redacted]	**£197,641**		[redacted]	**£204,894**	
1	60% severe hyperphagia, 40% moderate at baseline	[redacted]	**£234,346**	+£36,705	[redacted]	**£244,038**	+£39,144
2	2% treatment discontinuation	[redacted]	**£196,907**	-£734	[redacted]	**£205,095**	+£201
3	[redacted]% of patients moving to mild hyperphagia, and [redacted]% to moderate	[redacted]	**£223,296**	+£25,655	[redacted]	**£232,406**	+£27,512
4	Children who respond to treatment have [redacted]-level reduction in BMI-Z / BMI class	[redacted]	**£213,230**	+£15,589	[redacted]	**£218,105**	+£13,211
5	Number of carers for adults = 0.5	[redacted]	**£204,189**	+£6,548	[redacted]	**£213,920**	+£9,026
6a	BBS utility multiplier 0.9	[redacted]	**£181,684**	-£15,957	[redacted]	**£188,157**	-£16,737
6b	BBS utility multiplier 0.7	[redacted]	**£219,423**	+£21,782	[redacted]	**£228,382**	+£23,488
7	Updated physician monitoring visit costs and an additional visit in years 2+	[redacted]	**£197,992**	+£351	[redacted]	**£205,467**	+£573
8	1% waning of treatment effect	[redacted]	**£204,469**	+£6,828	[redacted]	**£211,949**	+£7,055
9	80% setmelanotide response rate	[redacted]	**£199,222**	+£1,581	[redacted]	**£207,582**	+£2,688
10	Corrected mapping of PedsQL to BMI health states	[redacted]	**£170,429**	-£27,212	[redacted]	**£176,161**	-£28,733
11	Corrected mapping of PedsQL for BBS multiplier	[redacted]	**£187,989**	-£9,652	[redacted]	**£194,671**	-£10,223

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported. BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental undiscounted QALY gains	QALY weight	ICER threshold applied to discounted ICER
Less than or equal to 10	1	£100,000 / QALY
11 to 29	Between 1 to 3 (equal increments)	£100,000 to £300,000 / QALY (equal increments)
Greater than or equal to 30	3	£300,000 / QALY gained

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

QALY weighting

Incremental QALYs versus best supportive care (probabilistic ICERs):

Deterministic analyses	Incremental QALYs - undiscounted	Discounted ICER (PAS) (/QALY gained)
Company base case		
Paediatrics	[redacted]	£197,641
Adults	[redacted]	£229,614
Mixed population	[redacted]	£204,894
EAG preferred base case		
Paediatrics	[redacted]	£203,784
Adults **(Most pessimistic QALY gain)**	[redacted]	£222,857
Mixed population	[redacted]	£208,457
EAG scenarios		
Most optimistic QALY gain: EAG's correction of the company scenario mapping PedsQL to EQ-5D for BMI health states in paediatrics	[redacted]	£170,429

- Can QALY weighting be applied to the company and EAG base cases?

*costs and benefits discounted at 3.5%. † Discounted ICER with no additional weighting reported. BMI, body mass index; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Other considerations

NICE

Equalities and innovation

Equalities:

- Setmelanotide indicated for use in children (aged 6 years of age and above) and adults
- Clinical and patient experts highlighted that:
  - ❖ People with BBS are visually impaired and may have poor co-ordination and/or reduced fine motor skills: need support to administer treatment (injection) & may disadvantage people who live independently /whose carer is not willing or able to administer treatment
- NHS England: Setmelanotide needs confirmatory genetic test
  - ❖ 20% of BBS population do not have identifiable pathogenic variants and are diagnosed clinically

Innovation:

Clinical experts: Important step for people with monogenic obesity and high unmet need in population

- ❖ Setmelanotide already approved for treating obesity caused by LEPR or POMC deficiency: incremental, but important development.
- ❖ Only drug to work on the MC4R pathway

Patient experts: current treatments do not address hyperphagia which significantly impacts wellbeing and QoL

- Are there any potential equalities issues that should be considered for setmelanotide?
- Does setmelanotide represent a step change in treatment?

QoL, quality of life; LEPR, leptin receptor; POMC, Proopiomelanocortin

Managed access

Conclusions from the managed access team

The company has not submitted a managed access proposal, which means that the committee cannot make a recommendation for managed access as things stand

- Further data collection around longer-term BMI-Z / BMI reduction would be feasible through the RM-493-022 long term safety and tolerability study.
- However, the managed access team feel the study is potentially biased (single-arm) and therefore it would be difficult to determine whether any potential reduction in BMI-Z / BMI is **caused** by setmelanotide.
- Any bespoke data collection arrangement to collect key model outcomes, such as BMI, in clinical practice may not be feasible or proportionate to the clinical uncertainties. This would require time to explore, design and implement.
- All other uncertainties, including those with higher impacts on ICERs, cannot be resolved through further data collection

BMI, body-mass index; ICER, incremental cost-effectiveness ratio

Decision making framework

1	What are the committee's preferred assumptions on: ❖ Baseline hyperphagia distribution ❖ Treatment effect on BMI-Z (number of class level drops) ❖ Treatment effect on hyperphagia ❖ Discontinuation rate ❖ Long term treatment effect (inclusion of waning effect) ❖ Sources for BMI/BMI-Z health state utilities ❖ Source for BBS utility multiplier
2	• What is the committee's preferred ICER threshold?
3	• Should QALY weighting apply?
4	• Therefore, using bullets 2+3, what is the committee's preferred ICER? • Which population should be used for decision making?
5	• Is the ICER below the preferred ICER threshold? If yes, can this be recommended for routine commissioning (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold)?
6	If not, could the key uncertainties be sufficiently resolved during a period of managed access? If so: • Has the company made a managed access proposal? Is this considered feasible? • Has the committee answered the questions in NICE's feasibility assessment? • What is committee's preferred threshold for managed access? • Which ICERs/assumptions represent committee's lower/upper end of uncertainty?
7	• What, if any, are the key remaining uncertainties?