NICE National Institute for Health and Care Excellence

Part 1	No academic and commercial in confidence
Public handouts	

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

1st Evaluation meeting

Lead team presentation

Chair: Peter Jackson

Lead team: Paul Arundel, Ron Akehurst, Jeremy Manuel

Evidence Review Group: Peninsula Technology Assessment Group (PenTAG)

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Company: Rhythm Pharmaceuticals

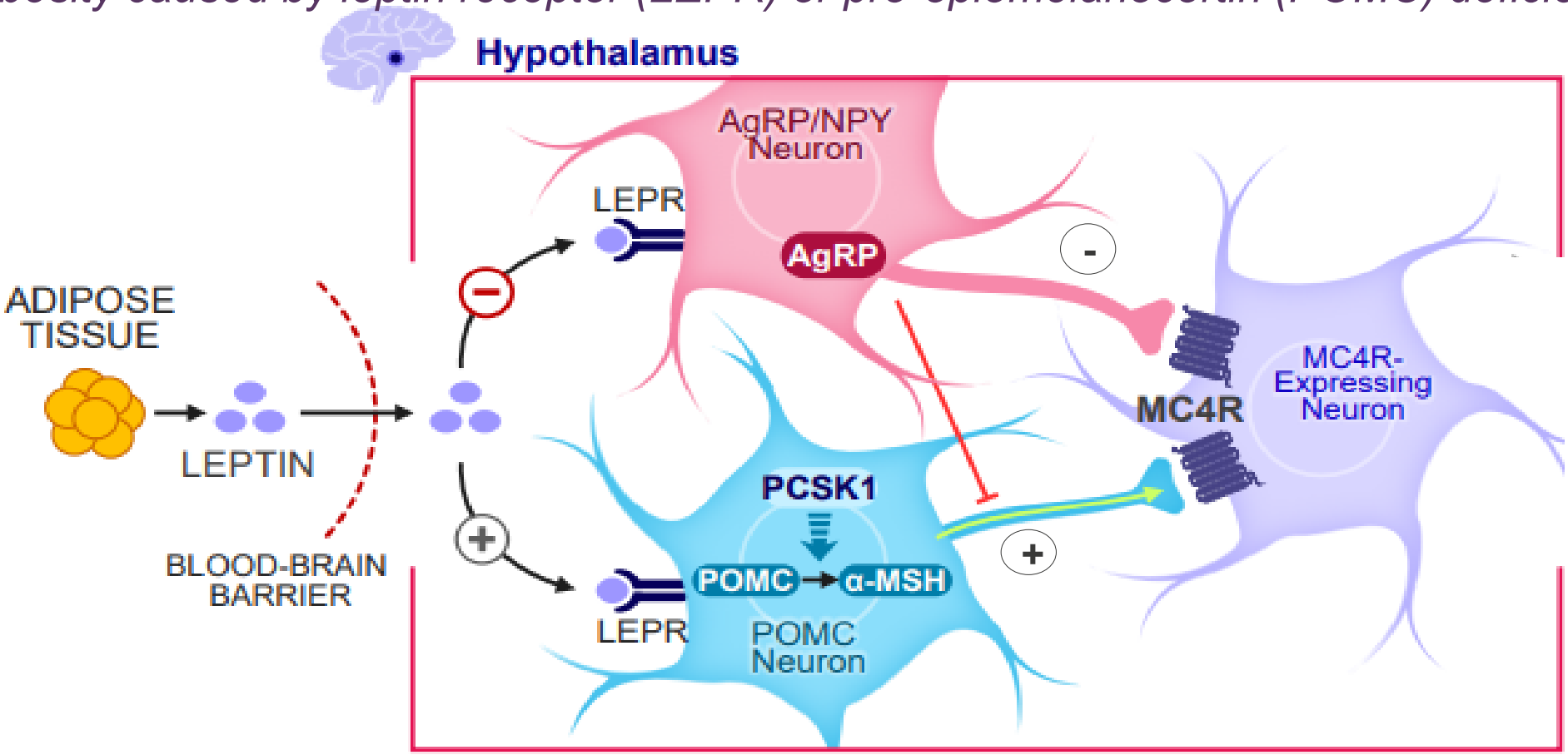
9th December 2021

Key issues, clinical effectiveness

Treatment pathway	*Company positions setmelanotide as 1st line treatment for LEPR/POMC obesity.* • How are LEPR and POMC deficiencies currently diagnosed? • What treatment do people with LEPR and POMC obesity currently have? • What is the committee's view of the proposed positioning of setmelanotide?
Population	*Clinical trials are small with strict exclusion criteria and few UK patients* • Are results generalisable to the population in the NHS?
Intervention	*Clinical trials recruited people from countries with different dosing schedules than licenced in UK* • What is the committee's view on dosing differences between the trials and marketing authorisation? How does this impact their generalisability to NHS practice?
Comparator/ comparative effectiveness	*Company excludes orlistat, methylcellulose and bariatric surgery as comparators* • What is the committee's view of excluding these comparators?
	There is no direct clinical evidence on the modelled comparator, standard management • Can committee judge the treatment effect of setmelanotide relative to best supportive care?
Clinical effectiveness	*Clinical evidence comes from small single-arm studies* • What is the committee view on setmelanotide's treatment effect on: body weight loss; reduction in BMI; hunger, and quality of life?
	Clinical trials exclude several scoped outcomes • What is committee's view on the absence of clinical evidence on setmelanotide's treatment effect on: mortality; hyperphagia (assessed indirectly through hunger scores only); and other outcomes listed in the NICE scope?
	Short total treatment duration (52 weeks) but extension study results suggest a plateau of effect • What is the committee's view on the long-term treatment effect of setmelanotide? • Do results suggest a waning of treatment effect?
	Differences in treatment effect observed by deficiency type • Should subgroups be considered separately based on deficiency type?

Disease background (1)

Obesity caused by leptin receptor (LEPR) or pro-opiomelanocortin (POMC) deficiency



- **Rare genetic disorders of obesity (RGDOs)** include hypothalamic disorders affecting melanocortin-4 receptor (MC4R) neuroendocrine system which regulates hunger, satiey and engery expenditure
- **Condition caused by** mutation in alleles of genes encoding LEPR or POMC/ proprotein convertase-subtilisin/kexin type-1 (PCSK1)

AgRP, Agouti-related protein; MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1

*Source: Company submission, figure 4

Disease background (2)

Characterised by early-onset, severe obesity and hyperphagia

Conditions with disruption of MC4R pathway are characterised by both:

- early onset, severe obesity, and
- hyperphagia: an overwhelming, heightened and relentless hunger mimicking feelings of starvation, longer time to reach, and shorter duration of, satiety

Diagnosis: poorly diagnosed

- genetic testing for rare genetic obesity available in NHS

Incidence/prevalence: UK prevalence unknown

- *Company*: [redacted] patients currently eligible for setmelanotide in UK. Incidence uncertain but company estimates between [redacted] patients eligible for treatment each year.*

*Source: Company budget impact analyses

Disease background (3)

LEPR and POMC deficiency associated with significant QoL impact; no specific treatments

Comorbidities: similar to general obesity but more severe comorbidity profile with deficiency specific symptoms:

POMC/PCSK1 deficiency	LEPR deficiency
• red hair • adrenal insufficiency • pale skin	• compromised immune system • deficient sex hormone and cortisol production leading to delay/absence of puberty • metabolic dysfunction • hyperinsulinemia

Quality of life (QoL): obesity and hyperphagia key factors affecting QoL; related fertility and reproductive issues, depression, social isolation and social stigma.

Mortality: scarce data;

- LEPR associated with particularly severe obesity: significant mortality rate in childhood due to respiratory infections

Treatment options: no specific treatment pathway,

- no guidance for the condition; treatment limited to diet and lifestyle advice, current guidelines/guidance focus on general obesity

NICE

QoL, quality of life

Setmelanotide, Imcivree®

Licenced for genetically confirmed biallelic deficiencies only; dose titration varies for adults and children

Marketing authorisation	EU marketing licence granted July 2021 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**"*
Mechanism of action	Activates the MC4R neuron, which decreases appetite and increases feelings of satiety
Administration	Subcutaneous injection into abdomen, thigh or arm, different site; once daily
Dosage	Summary of product characteristics details daily dosing based on age:

Age, years	Weeks 1-2	3 weeks onwards*	6 weeks onwards	Insufficient clinical response and previous dose well tolerated	
6 to < 12	0.5 mg	1 mg	2 mg	2.5mg	
>12	1 mg	2 mg	N/A	2.5 mg	3 mg

**If starting dose well tolerated, dose can be increased after 2 weeks. If dose escalation not tolerated, starting dose maintained*

Duration	Long-term use
List price	List price £2376 per 10mg vial. Total annual costs per patient [redacted] (year 1), [redacted] (years 2+)*

MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase-subtilisin/kexin type-1 *Source: Company budget impact analyses

Background: measuring BMI

Company includes patients with severe obesity only; measured using BMI-Z score in children

Children

- Complicated to measure BMI as still growing.
- Use **BMI-Z score adjusted for age and sex** to asses weight against average growth score.

BMI-Z classes in children

Class	Percentiles		BMI-Z scores (SDs from the mean)	
	Min	Max	Min	Max
Normal	15th	84th	0	0.99
Overweight	85th	94th	1	1.99
Obese	95th	98th	**2**	**2.99**
Morbid obesity	99th	N/A	**3**	**N/A**

Source: adapted from WHO growth charts – 0-5 and 5-19 years

- Company: BMI-Z score reduction of ≥0.15 to 0.2 normally considered clinically important difference*
- Children with LEPR/POMC obesity **can have a BMI-Z score of >4**

Adults

- RGDOs often epidemiologically characterised by severe obesity or obesity class III

BMI classes in adults

Class	BMI, kg/m²	
	Min	Max
Overweight	25	29.9
Obesity I	**30**	**34.9**
Obesity II	**35**	**39.9**
Obesity III	**40**	**N/A**

Source: NICE clinical guideline 189: Obesity: identification, assessment and management

*Source: company submission references Ells LJ et al., Bibbins-Domingo K et al., Wiegand S et al. and Kirk S et al. **Red** denotes BMI/BMI-Z scores included in company's population. BMI, body mass index, RGDO, rare genetic disorders of obesity; SD, standard deviation

Diagnosis for POMC/PCSK1 or LEPR deficiency

Testing routine, but triggered by poor response to diet and exercise interventions

Genetic testing recently commissioned nationally

Clinical experts: diagnostic system (NHS genetic services) well established: numbers unlikely to increase with wider testing

ERG: expected wider rollout of genetic testing among children with severe obesity and diagnosed cases likely to increase

Testing currently triggered by poor response to standard lifestyle interventions

NICE Clinical Guideline 189*: recommends genetic testing only in people who would have surgery

Company: testing carried out by paediatric endocrinologist or geneticist based on:

- Extreme early onset obesity
- Hyperphagia
- Family history of extreme obesity

Specific treatment model needs to be established to allow genetic testing at diagnosis**.**

ERG: Testing children who present with early onset severe obesity could allow earlier access to treatment

◉ *How and when are LEPR and POMC deficiencies currently diagnosed?*

NICE

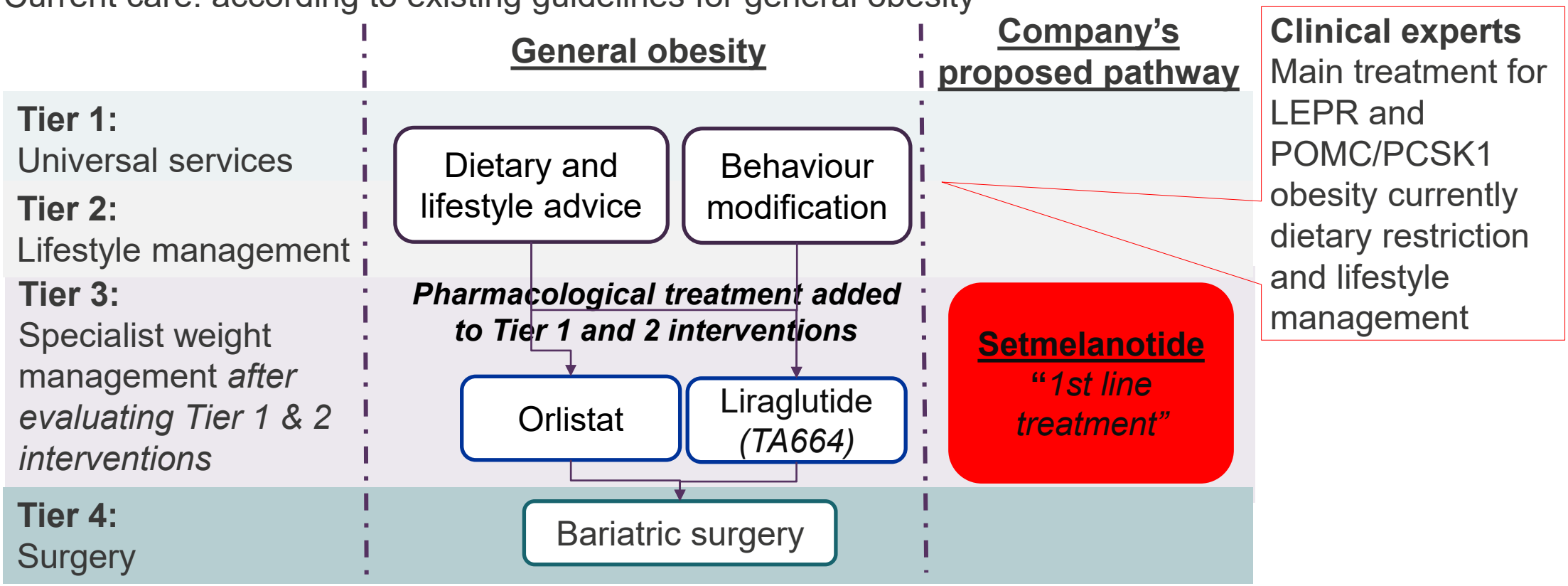
*NICE clinical guideline 189: Obesity: identification, assessment and management

Positioning in treatment pathway

Company: *setmelanotide offered along with tier 3 NHS management of obesity*

No existing guidelines or clinical pathways of care specific to LEPR or POMC deficiency.

Current care: according to existing guidelines for general obesity



ERG: Relevance of current guidelines to appraisal population limited: focus on general obesity

- Many recommended treatments not appropriate / effective: don't address MC4R pathway deficiency

- ◉ *What treatment do people with LEPR and POMC obesity currently have?*
- ◉ *How are services for people with the condition currently provided in practice?*
- ◉ *What is the committee's view of the proposed positioning of setmelanotide?*

Based on Obesity: identification, assessment and management (CG189) which recommends a tier-based system. MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase-subtilisin/kexin type-1

Decision problem (1)

***Company submission**: population narrower than scope; some comparators excluded*

	Final scope NICE	Company deviations	ERG comments
Population	LEPR or POMC obesity aged ≥6 years, with the following markers: • aged ≥18: BMI ≥30 kg/m2 • ≤aged 17: weight ≥97th percentile for age on growth chart	In line with marketing authorisation, including: 1. **Biallelic** LEPR or POMC deficiency **confirmed by genetic testing** only - > no heterozygous mutations 2. Children and adolescents with weight ≥ 95th percentile	Company's population **narrower than scope, reasonable**: 1. Includes only most severe obesity (biallelic): likely some people classed obese heterozygous for POMC mutations 2. 95th percentile acceptable - some eligible children may be below 97th percentile with rigorously managed food intake
Intervention	Setmelanotide	Setmelanotide with standard management	Reflects clinical practice
Comparators	Standard management without setmelanotide (including reduced calorie diet and increased physical activity), orlistat, methylcellulose, bariatric surgery	Excludes **orlistat, methylcellulose and bariatric surgery** as comparators	Deviation acceptable: • Excluded comparators not routinely used for this indication in NHS practice

◉ *What is the committee's view on the narrower population?*

BMI, body mass index

Relevant comparators for setmelanotide

***Company**: excluded comparators not used in clinical practice*

METHYLCELLULOSE AND ORLISTAT

Company: Not comparators: *do not treat underlying hyperphagia*

- Orlistat excluded as comparator in TA664 (liraglutide) and TA494 (naltrexone-buproprion) for managing overweight and obesity

Clinical experts: Methylcellulose not used in children, doesn't improve hyperphagia.

Orlistat may be used, but does not improve satiety, ***unlikely to result in clinically meaningful weight loss***. Poor adherence due to side effects.

ERG: ***don't have sufficient 'horsepower'*** to be efficacious for LEPR or POMC obesity

BARIATRIC SURGERY

Company: potentially harmful to reduce stomach size in someone with untreated hyperphagia

Weight regain post surgery common: existing neurohormonal appetite dysregulation persists

Clinical experts: Gastric banding and gastric sleeve surgery not used: require restriction of intake which may cause significant side effects with hyperphagia.

- Gastric bypass possible but ***usually only older patients***:
  - eventual weight regain, life-long risk of iron/vitamin deficiency, bone health issues.
- Poor outcomes in homozygous rare genetic obesity: possible for heterozygous variants

ERG: rarely used, ***considered dangerous*** in this population

Not meaningful to include in model: fundamental differences between surgical and medical treatment

◉ *What is the committee's view of excluding these comparators?*

Decision problem (2)

***Company** excludes some scoped outcomes; **ERG** prefers subgroups by deficiency and age*

	Final scope NICE	Company deviations	ERG comments
Outcomes	• BMI, BMI-Z • weight loss • percentage body fat • waist circumference • hunger • incidence of type 2 diabetes • cardiovascular events • mortality • co-morbidities including cancer • adverse effects of treatment • HRQoL: patients and carers	Company did not collect data on: • *carer QoL* • *mortality* • *cardiovascular events* • *co-morbidities including cancer*: life expectancy not long enough	Company's outcomes narrower than scope. • Lack of data not appropriate justification for exclusion of scoped outcomes.
Subgroups	None	None	Clinical advice suggests differences in natural disease progression by mutation type and disease state between adult and paediatric patients. ***Subgroup analyses most appropriate:*** a) LEPR (paediatric), b) LEPR (adult), c) POMC (paediatric), d) POMC (adult)

AE, adverse effect; BMI, body mass index; HRQoL, health related quality of life; SAE, serious adverse effect

NHS England and Improvement perspective

Clinical pathway poorly defined; setmelanotide administered through national centre

Pathway of care

- ***No effective pharmacological therapy*** in place for either condition: Setmelanotide would have a **substantial impact** on current pathway
- Due to rarity of condition, clinical pathway from local centres not well defined
- No NHS clinical commissioning policies for this indication

Current service provision

- No specific highly specialised service for this condition but ***one national centre of excellence*** and expertise in England.
- Genetic testing required to confirm diagnosis, but ***no additional investment required***

Patient and carer submissions

Nature of the disease

Multifaceted disease; challenging to control from childhood and associated with social stigma

Presentation

- Early-onset obesity apparent within the 1st few months of life: *'[he] was 4 years old and was the same weight as a regular 10 year old' 'every pushchair broke due to his size.'*
- Constant food seeking behaviour: *'He would steal food and eat at every opportunity.'*
- Commonly diagnosed late as condition extremely rare: lack of knowledge on rare genetic obesity

Symptoms

- Hyperphagia described as '*insatiable hunger….24 hours a day*': a basic survival instinct '*as powerful as the need to breathe and sleep*'
- Symptoms of extreme obesity concerning for carers and patients (e.g. increased risk of cardiovascular complications, diabetes, strain on vital organs)
- Associated comorbidities also challenging:
  - LEPR deficiency associated with a compromised immune system and regular infections: *'He became permanently unwell, suffering chronic ear infections and colds'*
  - Deficient testosterone levels during puberty affect normal growth

Psychosocial aspects

- Social stigma caused by poor understanding of rare genetic disorders of obesity:
  - Children often bullied at school and struggle with normal activities (e.g. sports, buying clothing): impacts educational attainment
  - Leads to poor mental health, including depression, and low self-esteem
- ***Quality of life impact for carers:*** accused of overfeeding children, anxiety about being unable to control food intake can negatively impact close relationships

Current treatments for the condition

Current treatments not sustainable or effective on long-term basis

Unmet need for new treatments

Currently no effective treatments for obesity associated with LEPR or POMC deficiency: *'we had the diagnosis, but there wasn't a solution'*

- Gastric band ineffective in this population: satiety messaging pathway from the stomach to the brain is disrupted so hyperphagia continues.
- Diet and exercise modification does not manage the obesity:
  - Challenging for carers to implement a strict diet and exercise regime
    - '*We were advised to restrict his daily calorie intake to 600 which proved almost impossible'*
    - *'I made his food from scratch to give best nutritional value whilst restricting calorie intake to try and stabilise weight gain.'*
    - Burden of daily care '*physically and mentally draining'*
    - Supporting exercise, food and a healthy lifestyle increasingly difficult in teenagers: *'I lost control over what he ate and he gained 1 stone/year'*
  - Requires *'planning, organisation, control, and sheer determination'* by both patients and carer

Experiences of setmelanotide

Setmelanotide 'life-changing' with manageable side effects

Advantages of the technology

- Improves all aspects of the condition including hyperphagia: '*he no longer feels permanently hungry'*
- Associated mental health and self-esteem improvements results in healthier personal relationships
- Early diagnosis and treatment could reduce disease impact and offer opportunities currently unavailable to patients (e.g. access to education)
- People lose weight when exercising with setmelanotide: not associated with standard management
- Cost savings for patients and their families associated with reduced food bill
- Patient states that *'the advantages far outweigh the disadvantages'* and that setmelanotide allows people with the condition to '*lead a normal life'* and have *'a normal relationship with food*'
- *'Achievement is not restricted by physical limitation, emotional wellbeing or unconscious bias'*

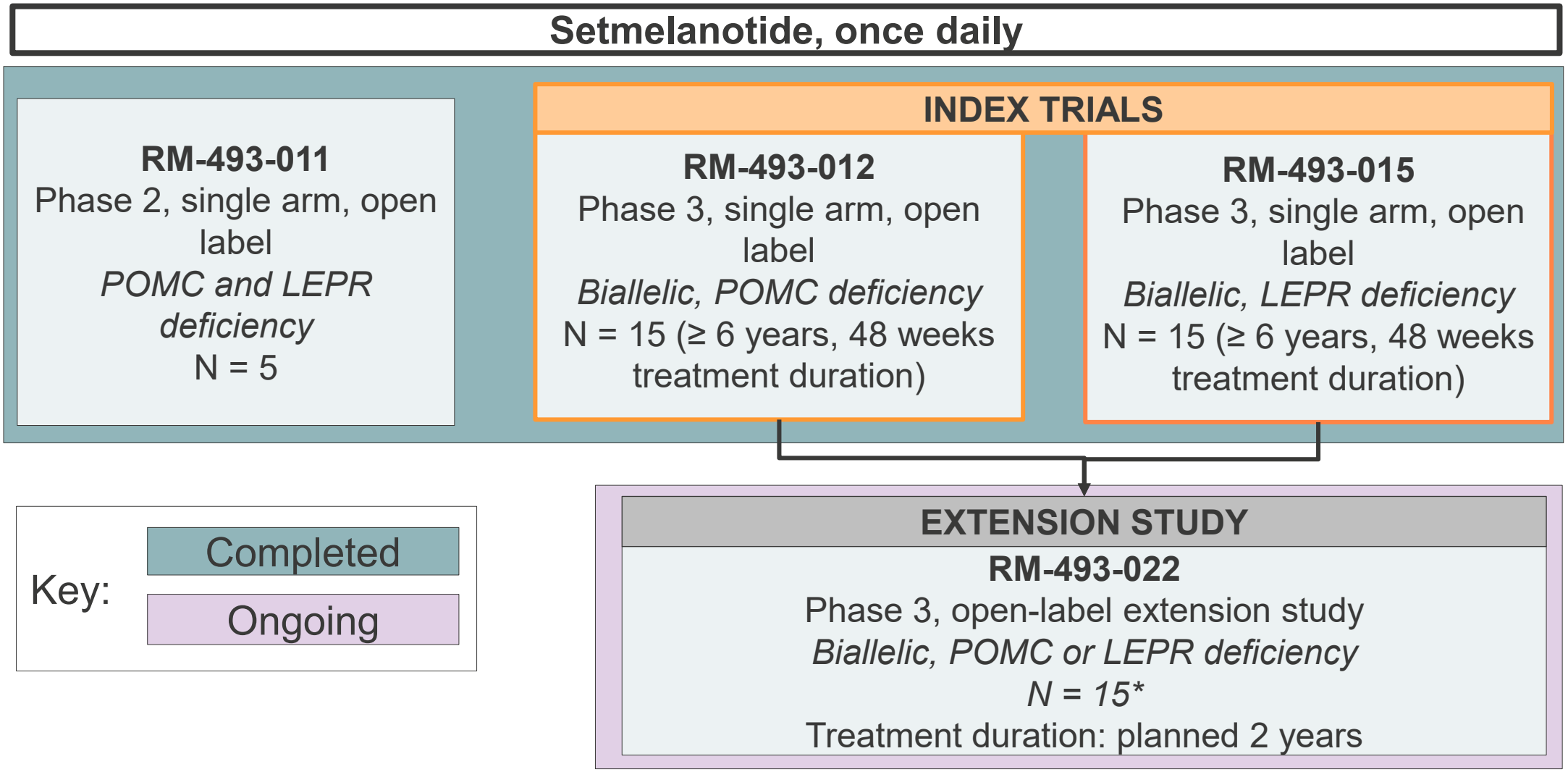
Administration

- Easy to administer as subcutaneous injection, either by the patients or carers
- Potential disadvantages include:
  - Temporary pain from injections and bruising around injection sites.
  - Difficulties when travelling: ensuring appropriate cold storage, privacy to inject daily, carrying medical documents to prove the need for treatment
  - Side effects including: aching joints during initial treatment; occasional dehydration headaches due to reduced hyperphagia; significant darkening of skin and hair *NB: some patients consider hyperpigmentation an advantage*.
  - Mode of administration may be challenging for people with fear of needles or pain

Clinical effectiveness evidence

Clinical trials

Small single arm trials for setmelanotide; no natural history studies identified



No natural history studies identified. Clinical effectiveness for best supportive care informed by expert opinion.

* Extension study also includes people with other genetic defects upstream of MC4R, such as Smith-Magenis Syndrome and SH2B1 deficiency obesity. Numbers reported here relate to POMC/PCSK1 and LEPR patients only

Clinical trials: study schema

Single arm trials with blinded withdrawal phase followed by optional extension study

INDEX TRIALS RM-493-012 & RM-493-015

Phase	Dose titration	Open label treatment	Blinded withdrawal phase	Open label treatment
Duration (weeks)	Variable: 2 -12	12	8	32
	Total: 52 weeks			
	Starting dose: - Adults: 1.0 mg - Children 0.5 mg* *2 weekly 0.5 mg dose increases to max 3.0 mg**	Includes last 2 weeks of titration phase at individualised therapeutic dose	• 4 weeks placebo, 4 weeks setmelanotide • Timing of placebo variable to mask actual timing of setmelanotide withdrawal	

Optional entry to extension study

***RM-493-012:** Germany and France: Starting dose 0.25 mg in children, max dose of 2.5 mg in adults

RM-493-015: Germany: starting dose 0.25 mg in children, max dose of 2.5 mg in adults. France: max dose 2.5 mg in adults, adjusted to 3.0 mg during trial.

RM-493-022

Open label treatment with setmelanotide

Further 2 years at therapeutic dose for patients from:

- RM-493-012 (POMC) N = 9
- RM-493-015 (LEPR) N = 6

Clinical trials: population

Heterogeneity in trial populations; ongoing extension study to complete March 2023

	RM-493-011	RM-493-012	RM-493-015	RM-493-022
Population	Genetic defects upstream of MC4R including: • POMC (homozygous, heterozygous) N=2*, • LEPR N=3	Biallelic loss of function POMC/ PCSK1 mutations N=15	Biallelic, homozygous/ compound heterozygous loss of function LEPR mutations N=15	Genetic defects upstream of MC4R, including: • POMC/PCSK1 N=9 • LEPR N=6
Status	Completed	Completed		Expected completion Mar 23

**plus 2 patients with epigenetic (hypermethylation) POMC variants. Excluded from licence so not referred to further.*

MC4R, melanocortin 4 receptor

Clinical trials: trial design

4 week self-control with placebo in index trials; planned max. treatment duration ~3 years

	RM-493-011	RM-493-012	RM-493-015	RM-493-022
Design	Phase 2, single-arm, open-label pilot	Phase 3, single-arm, open-label study		Phase 3 extension study
Control	None	4 week placebo withdrawal / self-control		None
Treatment duration	12-13 weeks	48 weeks		2 years planned, results from max 89 weeks
Dose	Individualised therapeutic dose: max 2.5 mg	Individualised therapeutic dose: adults max 2.5 -3.0 mg, children max 2.5 mg		Individualised therapeutic dose from previous trial
1º endpoint	% change in body weight & BMI	% of patients achieving ≥10% weight loss, baseline to ~1 year		Frequency and severity of AEs
Key inclusion criteria	≥6 years, BMI ≥ 30 kg/m^2 (>95th percentile if <18 years)	≥6 years (≥12 years France); BMI ≥ 30 kg/m^2 (>97th percentile if <18 years)		≥6 years, completed previous setmelanotide trial
Key exclusion criteria	No successful diet and exercise regime within 2 months; no prior gastric bypass resulting in >10% weight loss; no suicidal ideation			No suicidal ideation
In model?	No	**YES**	**YES**	No

BMI, body mass index

Clinical trials: baseline characteristics

Small trial populations; few UK LEPR patients, no UK POMC patients

	RM-493-011	RM-493-012	RM-493-015	RM-493-022 (POMC/PCSK1 only)*
Population (n)	[redacted] – results from 5 only	15	15	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 (7)	22 (9)	18 (4)
% female	[redacted]	40	60	43
Deficiency (n)	POMC [redacted], LEPR [redacted], Epigenetic [redacted]	POMC (13) PCSK1 (2)	LEPR	POMC/PCSK1
Weight (kg), mean (SD)	[redacted]	111 (36)	132 (39)	92 (18)
BMI (kg/m^2) mean (SD)	[redacted]	39 (8)	49 (13)	30 (7)
Morning Hunger Score†, mean (SD)	[redacted]	[redacted]	[redacted]	NR
Most hunger score† (SD)	NR	NR	[redacted]	[redacted]
IWQOL-Lite score, mean‡ (SD)	NR	[redacted]	[redacted]	NR

*demographics not provided for the 6 LEPR patients included in RM-493-022 (nationality unknown). † hunger score measured on a Likert scale of 0 (no feeling of hunger) to 10 (extreme hunger). ‡ IWQOL based on a scale of 0 (worst quality of life) to 100 (best quality of life). BMI, body mass index; IWQOL, Impact of Weight on Quality of Life; SD, standard deviation. Source: ERG report, table 11

Population

ERG: *generalisability of population in company's trials to NHS uncertain*

Population	<u>Strict in/exclusion criteria likely excluded people who would benefit from treatment</u> *Small population in pivotal trials.* RM-493-012 and -015 excluded people who had: • successful gastric bypass surgery • lost or maintained weight through diet and exercise within 2 months • depression (Patient Health Questionnaire-9 score ≥15) or severe suicidal ideation • severe renal impartment Given the nature of the condition (especially LEPR which is more severe), people likely to meet at least one of these criteria
	<u>Generalisability of trials to NHS population uncertain</u> • Small patient numbers, no external control group and lack of UK patients • Paediatric efficacy and safety unknown: 1 patient in trial RM-493-015 was under the age of 12; youngest patient in RM-493-022 was ** years • All data in RM-493-022 clinical study report (except for hunger scores, where 6 patients with LEPR deficiency obesity were included) were from patients with POMC deficiency: likely to have lower life expectancy due to more co-morbidities, especially adrenal insufficiency -> might overestimate efficacy of setmelanotide
	<u>Appropriate to consider LEPR and POMC deficiencies in separate trials</u> • Outcomes and severity of obesity vary by gene mutation • Different comorbidities by mutation type

◉ *How generalizable are the trials to the population with POMC and LEPR deficiency in the NHS?*

BMI, body mass index; PCSK1, proprotein convertase-subtilisin/kexin type-1

Intervention: dosing

ERG: *dose titration in pivotal trials does not reflect schedule in the marketing authorisation*

Maximum doses in trials not consistent with intended UK dosing of 3mg daily

Lower maximum and starting doses in Germany

- **RM-493-015:** [redacted] of 11 ([redacted]%) people had 3.0 mg. All POMC patients from Germany -> max 2.5 mg dose.
- **RM-493-022:** ***Long-term efficacy & safety uncertain:*** all 7 POMC patients from Germany. ***No long-term evidence at UK max dose of 3.0 mg*** including safety data after 48 weeks and discontinuation rate
  - Ethnicity and treatment pathway variation beyond dosing unlikely to impact generalisability of results
  - Company should have ensured a more diverse population in extension study

Dose titration used in pivotal trials and marketing authorisation

	RM-493-012 and -015 (mg)			Marketing authorisation (mg)	
Week	>18 yrs	12-17 yrs	6-11 yrs	> 12 yrs	6-12 yrs
1-2	[redacted]	[redacted]	[redacted]	1.0	0.5
3-4	[redacted]	[redacted]	[redacted]	2.0	1.0
5-6	[redacted]	[redacted]	[redacted]	-	2.0 (from week 6)
7-8	[redacted]	[redacted]	[redacted]	-	-
9-10	[redacted]	[redacted]	[redacted]	-	-
11-12	[redacted]	[redacted]	[redacted]	-	-
Insufficient clinical response and previous dose well tolerated				2.5	**2.5**
				3.0	-

Bold donates max dosage for group. **Red** doses not available in Germany (and France for RM-493-012 and some of RM-493-015) Source: adapted from setmelanotide summary of product characteristics and RM-493-012 CSR.

Steeper up-titration regimen in marketing authorisation than RM-493-012 and -015

- Marketing authorisation has fewer steps.

Treatment duration in RM-493-022 changed from 5 to 2 years

- Counterintuitive given uncertainties (small cohorts, short follow-up time during initial trials)

◉ *What is the committee's view on dosing differences between the trials and marketing authorisation?*
◉ *Does the committee consider that the trials' dosing impacts their generalisability to NHS practice?*

PCSK1, proprotein convertase-subtilisin/kexin type-1; yrs, years

Comparators

***ERG**: no direct or indirect evidence on comparative effectiveness of setmelanotide*

Comparator	**<u>Single arm trials and no direct or indirect evidence comparing setmelanotide with standard management</u>**
	***Clinical effectiveness uncertain relative to standard management** (only modelled comparator) :*
	• Heightened by lack of published data in RGDOs -> clinical effectiveness of standard management uncertain: also precludes indirect treatment comparison
	  ○ *Key limitation of evidence base (and modelled outputs) but agree lack of evidence makes ITC impossible*
	
	• Setmelanotide co-administered with standard management in trials:
	  ○ Aligned with anticipated use but hard to generate comparative data without a randomised controlled trial

◉ *What is committee's view on the clinical effectiveness of setmelanotide compared with standard management?*

NICE

ITC, indirect treatment comparison; RGDO, rare genetic disorders of obesity

Outcomes used in trials

ERG: *inconsistency in outcomes across trials; no data on hyperphagia or mortality from trials*

Key Outcome	Trial Nº RM-493-				ERG comments
	011	012	015	022	
BMI	✓	✓	✓	✓	
BMI Z-score	x	✓	✓	✓	Children growing: reported weight loss may underestimate fat loss.
Mean % change in body weight	✓	✓	✓	✓	
% with ≥10% weight loss, baseline to ~1 year	x	✓	✓	x	Company's success definition (35% meeting endpoint) low.
Mean % change in 'most hunger' score', ≥12 years old	x	✓	✓	x	- Multiple different measures for hunger appropriate. - RM-493-011, 012 and 015: Likert scores. RM-493-022: Global Hunger Questions asked to patients (or carers for 6-11 years). - Trials unblinded: could bias towards setmelanotide
% with ≥25% reduction in 'most hunger' score	x	✓	✓	x	
Hunger score (patients and carers)	✓	✓	✓	✓	
Glucose parameters	x	✓	✓	✓	- No baseline oral glucose tolerance test for existing diabetes - Test for future incidence of diabetes may not be appropriate
Change in HRQoL, patients	x	✓	✓	✓	RM-493-022: only baseline HRQoL available at data cut
Safety and tolerability	x	✓	✓	✓	

Red = primary outcome in trial. BMI, body mass index; HRQoL, health related quality of life; n, number. Source: adapted from ERG report, table 9

ERG: Key scoped outcomes not captured in trials

Outcomes excluded: cardiovascular events, co-morbidities (lack of data on common disease complications) and mortality (key limitation of the evidence base).

- ***Trial likely too short*** *to capture outcomes:* ***increases uncertainty surrounding clinical effectiveness and model inputs****.*
- *Longer follow up would allow collection of outcomes .*

Clinical experts: important outcomes ***mostly captured*** in trials: e.g BMI improvement/ weight loss, hyperphagia reduction, improved metabolic outcomes.
Co-morbidities also important.

◉ *What is committee's view on the absence of trial evidence on outcomes listed in the NICE scope?*

Clinical effectiveness results

Summary of analyses sets: RM-493-012 and -015

Company present results from multiple data sets and cohorts for key trials

Company presented data from 2 cohorts:

- Published results for 10 POMC and 11 LEPR patients, termed the 'pivotal cohort'
  - Minimum N=10 needed for statistical significance in 1° endpoint at 94% power, α = 0.05 and 0.025 1-sided, with success defined as 50% of patients achieving ≥10% weight loss
- Unpublished results including a further 5 POMC and 4 LEPR patients, termed the 'total cohort'.
- **All results presented in this section are for the total cohort** unless otherwise specified.

3 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 with weight loss ≥5 kg (or 5% if body weight at inclusion <100 kg) over 12-week open-label treatment period and 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.

RM-493-022: ***ERG***: presents results from week 37 for POMC and no results for LEPR patients.

Results presented here are from the longest available follow up (from clinical study report rider):

- POMC/PCSK1 deficiency: week 89
- LEPR deficiency: week 25

1° endpoint results: weight loss, index trials

Weight loss seen for setmelanotide in index trials

	RM-493-012 (POMC)	RM-493-015 (LEPR)
Primary outcome (FAS)	**N=14**	**N=15**
Proportion of patients achieving ≥10% reduction in weight from baseline to **52 weeks** (%), 90% CI, p-value	**12 (86%) (61, 97) <0.0001**	**8 (53%)* (30, 76) <0.0001**
Other key outcomes (DUS)	**N=[redacted]**	**N=[redacted]**
Average weight at baseline, kg (SD)	109 (37)	140 (38)
Average weight at week 52, kg (SD)	79 (23)	123 (35)
Least Square mean % weight change form baseline at week 52, kg, SD, p value	-26 (10, p<0.0001)	-12 (17, p<0.0001)
Red results directly inform economic model. *Higher rate (60%) used in model: includes 1 extra patient who had a clinical response but didn't meet weight loss endpoint		

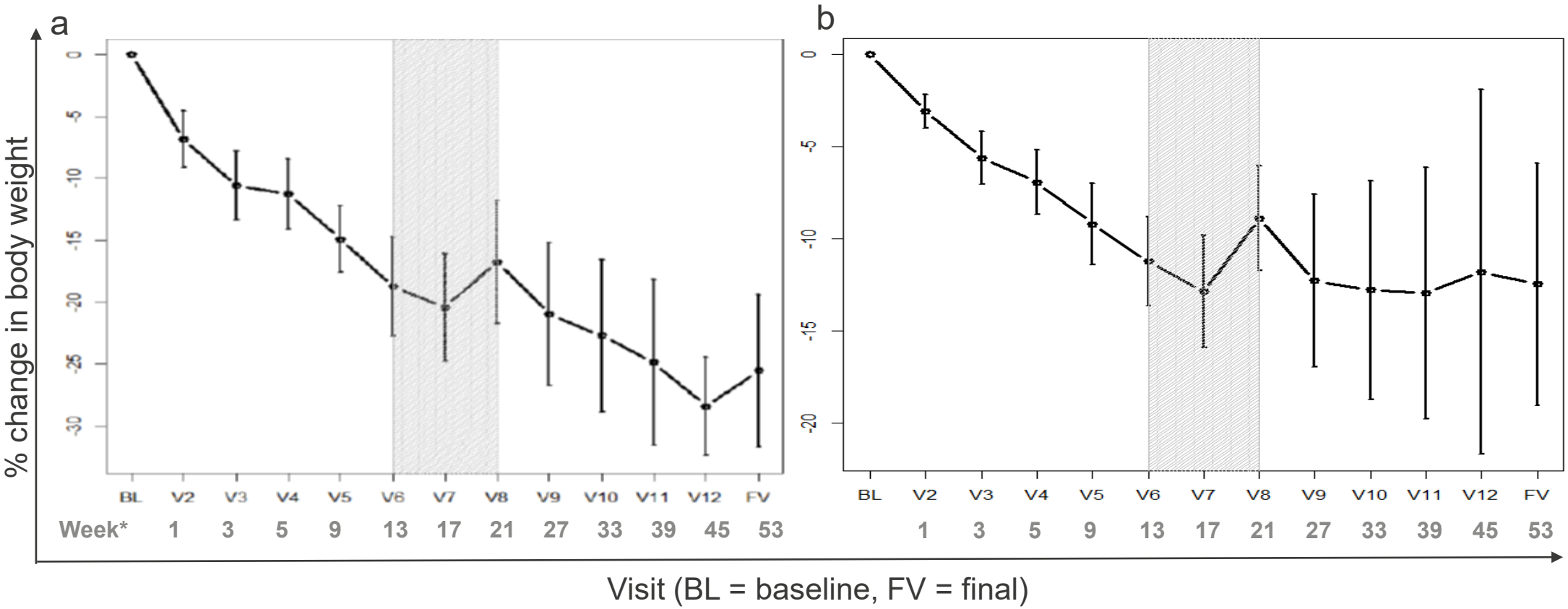
CI, confidence interval; DUS, designated use set; FAS, Full analysis set; kg, kilogram; SD, standard deviation.

Source: Table adapted from company submission, tables 28, 30, 39, 43

1° endpoint results: weight loss, index trials

Weight gain seen during the self-control placebo withdrawal period

% body weight change from baseline (pivotal cohort, DUS) a) POMC, b) LEPR patients



DUS	RM-493-012 (POMC)	RM-493-015 (LEPR)
Mean weight change in placebo withdrawal period, kilograms	**	**

**Irregular visit intervals in pivotal trials not shown on graphs*

NICE

Source: company submission Figure 11 and 14, tables 45 and 41

1° endpoint results: RM-493-011 and RM-493-022

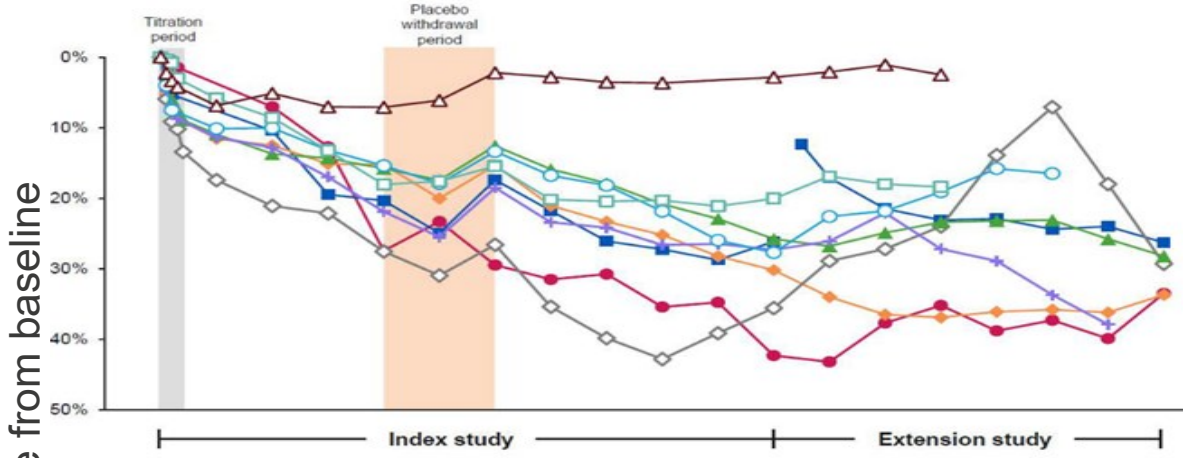
***ERG**: extension trial results suggest a plateau of weight loss with setmelanotide*

RM-493-011

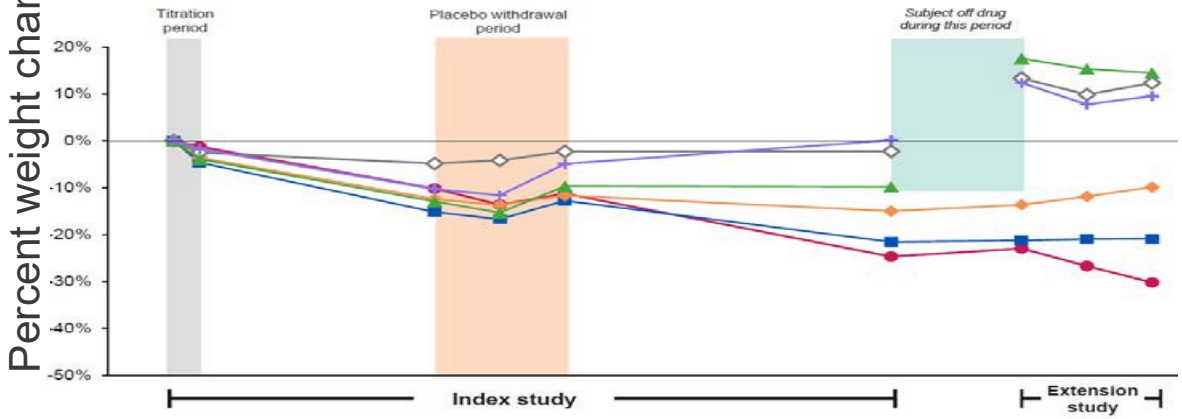
- POMC (N=2): mean weight loss ~15% at Week 12/13. [redacted] patient had ongoing weight loss at 4.4 years
- LEPR (N=5): patients lost weight on setmelanotide and gained weight during off-drug periods.

RM-493-022

Mean change in body weight for POMC/PCSK1 patients



Mean change in body weight for LEPR patients



Average weight at timepoint	Result
POMC/ PCSK1 (N=9)	
Extension study baseline, kg (SD)	84 (22)
89 weeks, kg (SD)	92 (21)
Absolute change from baseline, kg (%)	+8 (9)†
LEPR (N=6)*	
Extension study baseline, kg (SD)	122 (36)
25 weeks, kg (SD)	120 (38)
Absolute change from baseline, kg (%)	-2 (1) †

*Includes 3 patients who stopped setmelanotide for ~4.5 months between index and extension studies. † *calculated by technical team, statistical significance not tested*. SD, standard deviation

ERG: *possible waning effect*; company's reporting lacks clarity using "average (SD)" or "least square mean" between outcomes

Source: company submission, figure 17 & 18, tables 50 & 51

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

2° endpoint results: reduction in BMI

Reduction in BMI seen in index trials

Secondary endpoint (DUS): Reduction in BMI from baseline, kg/m²

	RM-493-011		RM-493-012		RM-493-015		RM-493-022
Latest data cut (weeks)	12-13		52				37
Population	*POMC*	*LEPR*	*POMC adults*	*POMC children (BMI-Z)*	*LEPR adults*	*LEPR children (BMI-Z)*	*POMC*
Baseline mean BMI (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BMI at latest data cut (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change (SD)	*-8 (1)*	*-4 (2)*	[redacted] *(NR)* ‡	[redacted] *(NR)* ‡	[redacted] *(NR)* ‡	[redacted] *(NR)* ‡	[redacted] *(NR)* ‡
% change (SD)	***-15 (2)***	***-9 (6)***	[redacted]	[redacted] ***(NR)*** ‡	[redacted]	[redacted] ***(NR)*** ‡	[redacted] ***(NR)*** ‡

Red results denote those informing the economic model. ‡*calculated by technical team so statistical significance not tested*. Source: adapted from RM-493-011, -012, -015, -022 clinical study report

ERG: Uncertainty in long-term treatment effect on BMI: increased in extension study:

- suggests plateau but only 5 of 7 POMC/PCSK1 patients had BMI reading after week 25

Similar results seen in both body fat and waist circumference, with limited further reductions in the extension study

◉ *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?*

BMI, body mass index; DUS, designated use set; kg, kilogram; m, meter; NR, not reported; PCSK1, proprotein convertase-subtilisin/kexin type-1.

2° endpoint results: daily worst hunger score

Improvement in hunger scores seen in index trials but plateau in extension trial

Secondary endpoint: Reduction in hunger score from baseline

	RM-493-011		RM-493-012*	RM-493-015*	RM-493-022	
Latest data cut (weeks)	*12-13*		*52*		*89*	*25*
Population	*POMC*	*LEPR*	*POMC*	*LEPR*	*POMC*	*LEPR*
Cohort			*Pivotal, DUS*	*Total, DUS*		
Baseline mean hunger score (SD)	10 (1)	9 (1)	8.1 (0.8)	[redacted]	[redacted]	[redacted]
Mean hunger score, latest data cut (SD)	1 (0)	3 (2)	5.8 (2.02)	[redacted]	[redacted]	[redacted]
Absolute change from baseline (SD)	*-9 (1)*	*-6 (2)*	*-2.3 (NR)* ‡	[redacted] *(NR)* ‡	[redacted] *(NR)*‡	*0.0 (1.3)*
Mean % change from baseline (SD)	***-89 (1)***	***-64 (17)***	***-27.1 (28.1) p=0.0005***	[redacted]	[redacted] ***(NR)*** ‡	[redacted]
Cohort			*Total, FAS*	*Total, FAS*		
Proportion of patients with ≥25% improvement in highest hunger score, N (%). (90% confidence interval), FAS	*NR*	*NR*	[redacted]	[redacted]	*NR*	*NR*

Red results denote those informing the economic model. ‡*calculated by technical team so statistical significance not tested*. Source: adapted from company submission, table 31, RM-493-011, -012, -015 clinical study report and -022 clinical study report rider.

ERG: For study RM-493-012, hunger scores in DUS total cohort identical to those in DUS pivotal cohort, which included 1 less patient. Unlikely to be correct.

- DUS population only includes responders to setmelanotide so may overestimate effect on hunger

RM-493-022 suggests results plateau with prolonged use of setmelanotide in POMC:

- marginal decrease of absolute change in hunger score of [redacted] in hunger score from baseline at 37 weeks

◉ *What is the committee's view on setmelanotide's treatment effect on daily worst hunger score?*

DUS, designated use set; FAS, final analysis set; NR, not reported

2° endpoint results: quality of life

*Improvements seen in key trials; **ERG**: lack of carer HRQoL significant uncertainty*

Secondary endpoint (DUS): Mean change in health related quality of life from baseline			
	RM-493-012*		**RM-493-015***
Latest data cut (weeks)	52		
Population	*POMC*		*LEPR*
HRQoL in adults, pivotal cohort (IWQOL-Lite)‡	*Adults,* [redacted]		*Adults,* [redacted]
Mean baseline IWQOL-lite score (SD)	[redacted]		[redacted]
Mean IWQOL-lite score at latest data cut (SD)	[redacted]		[redacted]
Absolute change from baseline (SD)	[redacted] *(NR)* †		[redacted] *(NR)* †
% change in score (SD)	[redacted]		[redacted]
HRQoL in children, pivotal cohort (PedsQL)‡	*Aged 8 – 12,* [redacted]	*Aged 13 – 18,* [redacted]	
% change in PedsQL score, carer and patient reported: mean (SD)	Carer: [redacted] Patient: [redacted]	Carer: [redacted] Patient: [redacted]	NR

† *calculated by technical team so statistical significance not tested*. ‡based scale of 0 (worst quality of life) to 100 (best quality of life).
Source: adapted from RM-493-012 and -015 clinical study reports

RM-493-011: POMC: 'dramatic' improvement reported (exact values NR). LEPR: HRQoL NR.
RM-493-022: HRQoL NR.

ERG: *Lack of HRQoL is a significant area of uncertainty*:

- No paediatric QoL data available at data cut for LEPR patients.
- Carer HRQoL not reported in trials

◉ *What is the committee's view on: a) setmelanotide's treatment effect on quality of life? b) the lack of evidence on carer quality of life?*

DUS, designated use set; HRQoL, health related quality of life; NR, not reported; SD, standard deviation

Results: adverse events (AEs)

Company: AE's not included in model because:

- Serious AE's not considered related to setmelanotide
- 1 death in RM-493-15 unrelated to treatment (car accident)

	Trial RM-493-			
	011 (N=[redacted])	012 (N=[redacted])	015 (N=[redacted])	022 (N=[redacted])
≥1 TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to study drug withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Commonly reported AEs				
Skin hyperpigmentation	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction*	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]

*includes erythema, oedema and pruritus. AE, adverse event; MC1R, Melanocortin 1 receptor TEAE, treatment emergent adverse event. Source: adapted from company submission, tables 54 – 62, RM-493-011 CSR, tables 16 and 19, RM-493-012 CSR, table 38, RM-493-015, table 31 and RM-493-022 CSR appendices, table 14.2.1.2A

ERG comments:

Inappropriate to exclude AEs from model

- RM-493-015: 1 withdrawal for grade 1 eosinophilia related to study drug.
- Rates of eosinophilia unknown: implication for real world use?

AEs associated with lifelong setmelanotide use uncertain

- Company use safety analysis sets (people with ≥1 dose study drug): broader than scope (e.g. epigenetic obesity)
- Key TEAEs not recorded in extension study despite high rates in index trials:
  - *Skin hyperpigmentation*: likely due to off-target interactions with MC1R. Undesirable for patients -> may withdraw from study drug
  - *Injection site reactions*: patient records suggest 100% of patients had injection site reaction during extension study.

Long-term TEAEs not fully captured in company's evidence

◉ *How tolerable is setmelanotide?*

Summary of results used in company's model

Company model includes key results for weight loss, BMI reduction and hunger score

	RM-493-012 (POMC)	RM-493-015 (LEPR)	Application in model
Directly inform the model			
1° outcome (FAS)	**N=14**	**N=15**	
Proportion of patients achieving ≥10% reduction in weight from baseline to 52 weeks	**86%**	53% **60%** used in model: accounts for 1 patient who responded clinically but didn't meet endpoint	**Response rates to setmelanotide*: put into model as 12 week data**
Indirectly inform the model			
2° outcomes (DUS)	**N=[redacted]**	**N=[redacted]**	
% reduction in BMI from baseline: mean	[redacted]	[redacted]	**Treatment effect on BMI**
% change in daily worst hunger score from baseline: mean (pivotal cohort only)	[redacted]	[redacted]	**Mapped to severity categories of hyperphagia**
** Equal response rates applied to both adults and children in the company's model*			

ERG: Company states that 12 week response rates to setmelanotide used in the model, but 12 week results not reported. Unclear whether results reported at 52 weeks were maintained from 12 weeks

◉ *Is it appropriate to use response at 52 weeks to inform response at 12 weeks?*

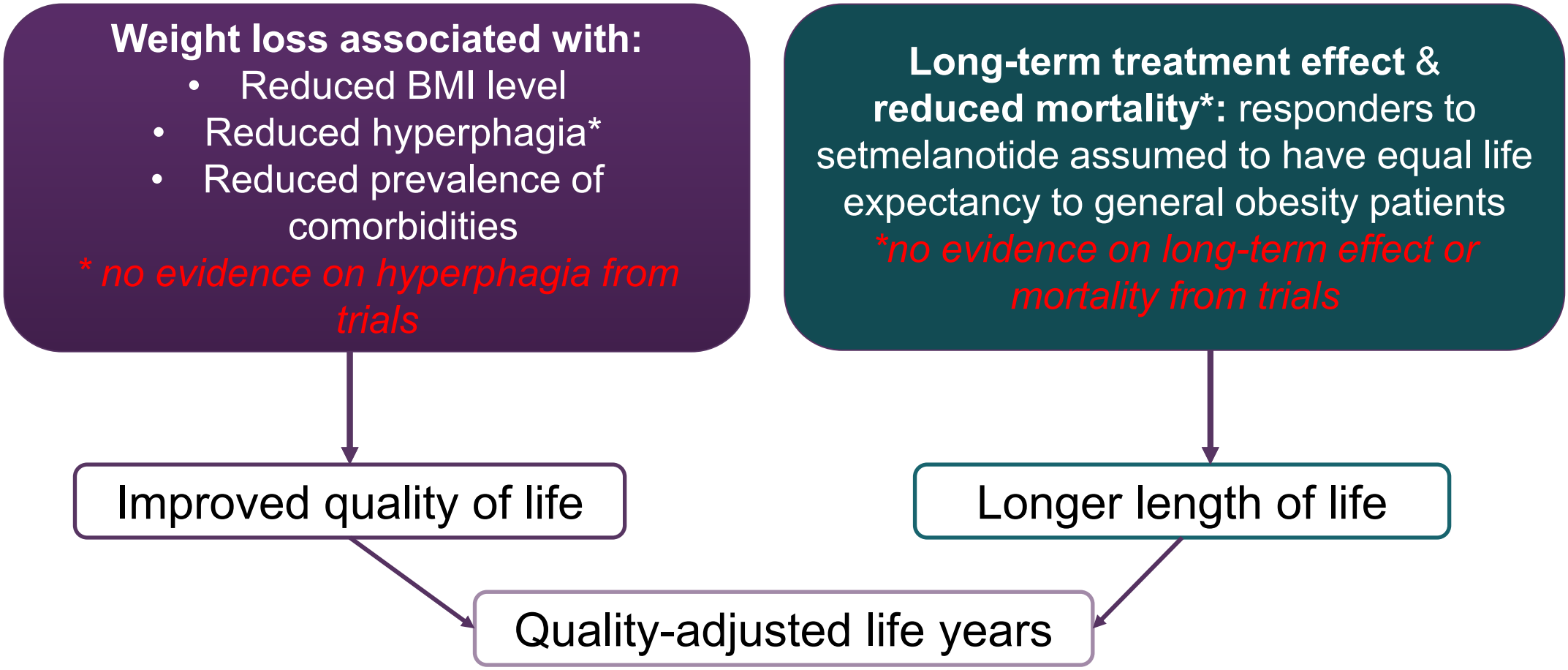
DUS, designated use set; HRQoL, health related quality of life; NR, not reported; SD, standard deviation

Cost effectiveness

Key issues, cost effectiveness

Model structure	*Company's model structure uses BMI health states and death. What is the committee's view on:* • The company's general model structure? • The modelling of BMI cut-offs and hyperphagia status? Is the company's model appropriate for decision making?
Population & subgroups	*The company uses the overall population for its cost-effectiveness analyses* • Are subgroup analyses based on age and/or deficiency type more appropriate for decision making?
Long term treatment effect	*The company' uses clinical expert opinion to inform long-term treatment effect and assumed no waning* • Would setmelanotide's effect on BMI and hyperphagia be maintained in long term?
Hyperphagia	*The company models a reduction in hyperphagia in setmelanotide responders* • What proportion of the population would have severe, moderate and mild hyperphagia at baseline? • What level of hyperphagia reduction is expected in responders to setmelanotide? • Should hyperphagia utility modifiers come from the company's vignette study or previous HST?
Mortality	*The company uses clinical expert opinion to predict life expectancy for setmelanotide non-responders and BSC, but general obesity mortality rates for responders* • Are these assumptions plausible? Has mortality been modelled appropriately?
Stopping treatment	*The company does not include stopping treatment in model* • Would people discontinue setmelanotide for reasons other than loss of response? If yes, at what rate?
Cost/dosing	*The company pools average adult and paediatric doses from trials to calculate treatment costs* • Should separate doses be used for adults and children in model?
Discounting	*The company uses a discount rate of 1.5% for benefits in its base case.* • Is this assumption appropriate, or should a discount rate of 3.5% be used?
QALY weighting	*Company and ERG base cases suggest significant QALY gains for setmelanotide compared with BSC* • Can QALY weighting be applied for this topic?

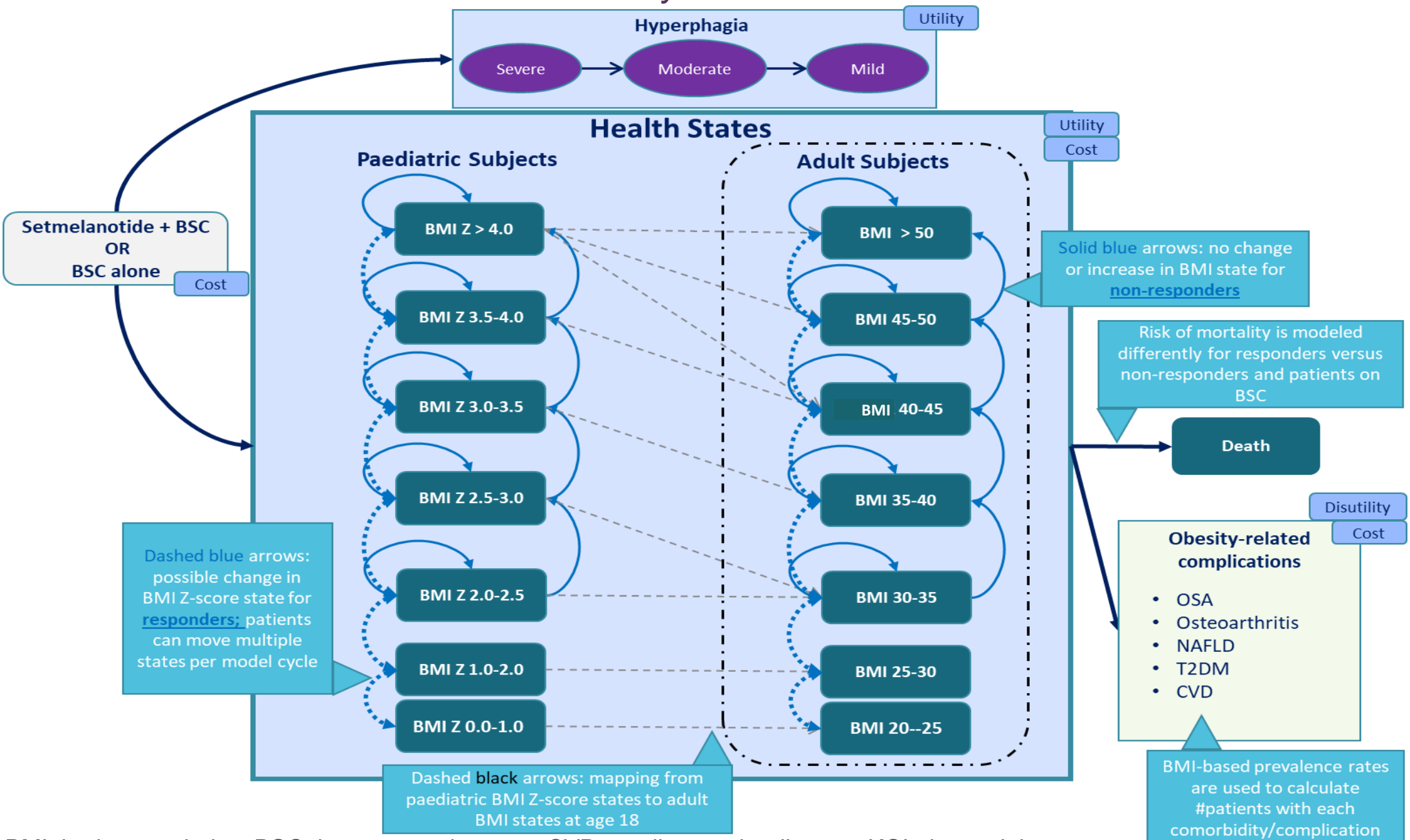
Overview: how quality-adjusted life years accrue for setmelanotide versus best supportive care



BMI, body mass index

Company's economic model

Markov model with health states stratified by BMI and BMI-Z scores



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. Source: company submission, figure 24

Company's modelling approach

Model structure	Markov state transition model
Population	LEPR and POMC/PCSK1-deficient paediatric/adult patients taking setmelanotide
Response to treatment	At **12 weeks**: responders or non-responders; Response rate: 86%* for POMC/PCSK1; 60%* LEPR
Intervention	Setmelanotide and BSC
Comparator	BSC
Cycle length	1 year
Time horizon	Lifetime
Health states	7 health states stratified by BMI/BMI Z-scores; death;
Transition probabilities	BMI the only modelled Markov state • Patients experience BMI gain as children • BMI-Z score states mapped to corresponding BMI health states when patients turn 18 years
Hyperphagia	Modelled as a utility multiplier assigned to BMI health states; independent from BMI states
Comorbidities	Modelled as disutilities applied to health states, which incur costs and increased risk of mortality
Discounting	3.5% for costs and 1.5% for benefits

**based on response rates from RM-493-102 and RM-493-015 at 52 weeks. LEPR response rate in trial = 53%. Higher rate includes extra patient who responded clinically but didn't meet weight loss endpoint.* BMI, body mass index

Model structure

Based on BMI/BMI-Z health states; structure differs from other recent obesity appraisals

Company: submitted a de novo Markov state-transition model with 7 BMI / BMI-Z health states + death

- Patients enter the model taking setmelanotide + BSC: week 12 onwards non-responders have BSC only
- Disutility and cost applied for common comorbidities in an additive manner
- Utility multiplier associated with hyperphagia status

ERG: Structure deviates from Ara et al. 2012, systematic review of drugs for obesity in primary care:

- informed model structure in NICE TA494 (Naltrexone–bupropion for managing overweight and obesity) and TA664 (Liraglutide for managing overweight and obesity)
- Company: Ara et al. 2012 excessively granular for T2DM and CV disease, insufficiently captures other key MCR4-related co-morbidities and early mortality vs. general obesity (especially for LEPR patients)

Company's model suitable for the decision problem but simplifying assumptions, especially related to hyperphagia, introduce uncertainty

◉ *What is the committee's view on company's general model structure?*

BMI, body mass index, CV, cardiovascular disease; T2DM, type 2 diabetes mellitus, TA, technology appraisal

Model structure: hyperphagia and BMI

__ERG__: company's model doesn't capture any interaction between BMI and hyperphagia status

BMI

- Company models pivotal trial 2º endpoint (BMI) as opposed to 1º endpoint (weight loss): BMI also not a key 2° endpoint in company's step-down evaluation to control for multiplicity in pivotal trials.
- When a patient turns 18, their BMI-Z score state is mapped to the corresponding BMI health state
  - BMI-Z health state >4.0 equally distributed across adult BMI 40–45, 45–50, and >50.
- LEPR/ POMC patients have *BMI gain as children*, no substantial BMI change as adults

Hyperphagia

- Modelled as a severity status: mild, moderate or severe
- *Hyperphagia status not impacted by BMI change* in model: modelled independently of BMI/BMI Z-score health state
  - additional complexity of modelling interaction requires more patient level data

ERG: *Model doesn't capture all relevant BMI health states*: max BMI health states are BMI >50 and BMI-Z >4.0 due to lack of data for severely obese patients with LEPR and POMC deficiency.

- Some patients fall into higher (more granular) BMI classes

ERG: *Impact of correlation between BMI class and hyperphagia status unexplored*: approach simplistic

- More granular than HST14 (Metreleptin for treating lipodystrophy) which applied a utility decrement based on presence or absence of hyperphagia only

◉ *What is the committee's view on company's modelling of: a) BMI (2° outcome) as obesity measure & cut-off choices, b) hyperphagia status independent from BMI heath states?*
◉ *Is the company's model appropriate for decision making?*

BMI, body mass index, HST, highly specialised technology

Population

***Company** models full population, **ERG** prefers subgroup analyses by gene type and age*

Company presents ICERs in ***overall population*** (combining gene type and age)

ERG: *overall population inappropriate* due to differences in:

- treatment effect and natural disease progression between POMC/PCSK1 and LEPR patients
- disease progression and related co-morbidities between adult and paediatric patients
- Not a clinically coherent patient group: ***prefer subgroup analyses by disease type and age.***

Modelled patient characteristics

- BMI baseline distribution (both adults and paediatric patients): RM-493-012 and RM-493-015
- Distribution of deficiency and age:

	POMC/PCSK1	LEPR	Source
Distribution	33.3%	66.7%	Graves et al, 2021
Adult	26%		Conference abstract by Argente et al 2019
Paediatric	74%		

Source: ERG report, table 16

ERG: Argente et al 2019 full study unavailable for review: unclear why conference abstract used over RM395-012 and -015 data, noted Aregente et al. included more patients

- Result not sensitive to scenario analyses using baseline distributions informed by pivotal trials. However, no results for subgroups by different distribution scenarios

◉ *Is the overall population or population by gene type and age more appropriate for decision making?*

ICER, incremental cost effectiveness ratio

Baseline hyperphagia severity distribution

Based on clinical opinion as not directly addressed in trials

Hyperphagia baseline severity distribution based on 1 clinical expert's opinion

ERG: company's estimates appropriate but:
- Unclear whether estimated distribution based on vignette descriptions of severity categories
- No company scenarios using alternative baseline distributions
- ERG scenarios vary baseline hyperphagia distributions

Baseline hyperphagia severity distribution by deficiency

Severity (Likert score)	Company (%) POMC	Company (%) LEPR	ERG* (%) POMC	ERG* (%) LEPR
Mild [redacted]	[redacted]	[redacted]	10	0
Moderate [redacted]	[redacted]	[redacted]	40	0
Severe [redacted]	[redacted]	[redacted]	50	100

*uses clinical advice to ERG. Source: ERG report, table 40

Company's vignette study

- 4 health state vignettes (no hyperphagia, mild, moderate, severe):
  - informed by literature & clinician perceptions (from interviews, existing company data)
- Health state vignettes included information on:
  - Subjective experience (e.g. meal size, satiety)
  - Observable behaviours (e.g. food seeking)
  - Impact (e.g. emotional, daily activities)
  - Weight
- Time trade-off (TTO) interviews with UK general population (n=215)
- Utilities elicited by TTO with 10-year time horizon

◉ *What is the committee's view on the company's vignette study?*
◉ *How do the modelled baseline hyperphagia distributions compare to clinical practice?*

Long-term treatment effect

Evidence from trials at 52-week follow-up; assumptions on long-term effect use clinical expert opinion

Effect on	1 year	2+ years	ERG comments	ERG scenario
BMI	***observed BMI reduction,*** week 52 RM-493-012 and -015 corresponds to: - POMC/PCSK1: [redacted] BMI level [redacted] - LEPR: [redacted] BMI level [redacted]	***no evidence from trials:*** clinical expert estimate: - POMC/PCSK1: [redacted] - LEPR: BMI [redacted]	***Paucity of robust clinical effectiveness data***: - Company's assumptions plausible but based on clinical opinion - need validating with robust long-term data	[redacted]& [redacted] after trial period, BMI-based response rates, smaller BMI [redacted]
Hyperphagia	- Change in hunger score (Likert scale 1–10) from trials mapped to hyperphagia severity status - Treatment effect applied at start of 1st cycle: assumed constant throughout treatment		***Area of considerable uncertainty*** - Probabilities use company analysis unavailable for critique -Treatment effect applied inappropriately: response measured at 12 weeks in trials. ERG apply at end of 1st cycle in base case.	Reduced impact of setmelanotide

Modelled treatment effect on hyperphagia severity

	Company model (%)			ERG scenario* (%)		
LEPR	Mild	Moderate	Severe	Mild	Moderate	Severe
Mild	[redacted]	[redacted]	[redacted]	100	50	50
Moderate	[redacted]	[redacted]	[redacted]	0	50	50
POMC						
Mild	[redacted]	[redacted]	[redacted]	100	40	33
Moderate	[redacted]	[redacted]	[redacted]	0	60	67

Source: ERG report, table 41

*Defined as [redacted]

BMI, body mass index

◉ *What is the committee's view on the appropriateness of the company's assumption on long-term treatment effect on BMI and hyperphagia?*

Mortality

No long term mortality data, expert opinion and general obesity rates inform life expectancy

Limited evidence and lack of widespread testing: mortality rates uncertain

- available data suggests poor expected mortality rates for LEPR and POMC/PCSK1 deficiency

	Company approach	ERG comments	ERG scenario
Responders	***Equal mortality to general obesity*** of similar BMI - HR's from general obesity applied to all-cause general population mortality rates (UK cohort study). Also mapped to BMI-Z scores. - Based on 1 clinical expert's opinion	***Likely worse mortality*** vs. general population: - LEPR: more vulnerable to infection - POMC: likely also have hypoadrenalism	No mortality benefit for responders
Non-responders and BSC	- Mortality rates estimated by 1 clinical expert transformed into ***probability distribution functions*** using beta distribution - Explored using Weibull and Gompertz	***Paucity of mortality data***: experts suggest company's estimates uncertain but reasonable. **Prefer:** company's scenarios with life expectancy converted to HR multipliers ([redacted] for POMC, [redacted] for LEPR) for consistency with company's responder mortality approach.	Company's mortality multiplier -10%; ↑ mean & max age life expectancy

Modelled mean and max age mortality, non-responders

	Company model		ERG scenario	
Life expectancy (years)	POMC	LEPR	POMC	LEPR
Mean age	[redacted]	[redacted]	45	50
Maximum age	[redacted]	[redacted]	55	60

Source: ERG report, Table 39

BMI-based HRs for all-cause mortality for responders to setmelanotide (adults)

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

Source: company submission, table 69

◉ *Is it appropriate to assume similar mortality risk stratified by BMI scores for responders and people with general obesity? Are life expectancy estimates for non-responders generalisable to NHS practice?*

BMI, body mass index, HR, hazard ratio; max, maximum

Stopping setmelanotide

Company did not include stopping treatment in model

Company:

Does not include a discontinuation rate for setmelanotide in the model because:

- No major discontinuation events related to setmelanotide in index trials or extension study
- Observed discontinuations were for causes deemed irrelevant to clinical practice or captured in 3 month response assessment.

ERG comment:

- Clinical advice suggests some patients likely to discontinue setmelanotide due to AEs (such as skin hyperpigmentation) and/or burden of daily injection administration.
- Discontinuations seen in pivotal trials relatively high: [redacted] discontinuation rate in RM-493-012
- ***1% discontinuation included in ERG base case,*** based on the rate in pivotal trial for TA664 (liraglutide for managing overweight and obesity). ERG assumptions:
  - Treatment discontinuation applies only to responders at 12 weeks.
  - Upon discontinuation, patients move to respective BMI state in non-responder arm -> same costs, hyperphagia utility distribution and survival rates as BSC.
  - Discontinuation rate applies only to 1 health state in the model, where highest % of people spend most time (differs by age and deficiency type)

◉ *What proportion of people would stop setmelanotide in clinical practice?*
◉ *Should stopping treatment be modelled? If so, Is the ERG's rate plausible?*

BMI, body mass index, HR, hazard ratio; max, maximum

Health-related quality of life

Utility values: sources in the company base case

IQWOL-lite and SF-36 collected in trials but not in model: company uses literature utilities

SF-36 ***not in base case:*** small sample size, non-standard collection timepoints, lack of generalisability to children, not specific hyperphagia measure

BMI z-score utility (children)

State	Utility	Source
0.0–1.0	0.89	PedsQL from Riazi et al. 2010 mapped to EQ-5D scale using Khan et al. 2014 for BMI-Z scores 0.0 -1.0 and 3.5 – 4.0. Other BMI-Z utilities extrapolated from these values.
1.0–2.0	0.87	
2.0–2.5	0.86	
2.5–3.0	0.85	
3.0–3.5	0.83	
3.5–4.0	0.82	
≥4.0	0.81	

Hyperphagia utility multiplier*

State	Utility	Source
Mild	[redacted]	Company vignette study
Moderate	[redacted]	
Severe	[redacted]	

BMI score utility(adults)

BMI	Age (years)							Source
	18–30	31–40	41–50	51–60	61–70	71–80	81+	
30–35	0.89	0.86	0.82	0.80	0.79	0.76	0.76	US study of SF-12 data for morbid obesity (Alsumali et al. 2018), mapped to EQ-5D
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	

*hyperphagia multiplier applied to each BMI/BMI-Z score health state weighted by the proportion of patients in each hyperphagia status (mild, moderate or severe). BMI, body mass index, EQ-5D, EuroQol-5D; PedsQL, Pediatric Quality of Life Inventory; SF-36, Short Form-36; US, United States. Source: adapted from company submission, tables 70-72

◉ *What is the committee view on the company's choice of utility values used in model?*

Comorbidities

Disutility for commonly occurring comorbidities applied at differing prevalence rates depending on BMI/BMI-Z score

Comorbidity	Prevalence*	Source	Disutility	Source	Assumption based on
Sleep apnoea	10 - 86%	Young et al. 2002, Lopez et al, 2008	**0.034**	Søltoft et al. 2009	Association between obesity and respiratory problems (assumed reflective of obstructive sleep apnoea).†
Osteoarthritis	6 - 27%	Ahmad et al. 2014	**0.187**		Association between musculoskeletal problems and HRQoL.†
Type 2 DM	3 – 23%		**0.043**		Association between T2DM and HRQoL.†
NAFLD	22 – 95%	Estes et al. 2018, Mummadi et al. 2008: Extrapolated to BMI states with no data.	**0.000**	Assumed disutility comparable to obesity	Clinical opinion to company
CV events	4 – 17%	Ahmad et al. 2014	**0.064**	Sullivan et al. 2011	Weighted average of disutility by CV event type and prevalence of each event

*min = prevalence in 20-25 BMI state and max = prevalence in >50 BMI state. †Disutility in model uses average of reported utility decrements by sex

CV, cardiovascular; DM, diabetes mellitus; HRQL, health related quality of life; NAFD, non-alcoholic fatty liver disease

Utilities, ERG comments (1)

Data source	• Reasonable to exclude SF-36 data from trials given data limitations • Acceptable to use general obesity utilities for BMI states but lack of stratification for BMI >50. Relevant as LEPR patients often immobile & inactive with limited social interaction
Utility modifier	***Hyperphagia multiplier uncertain:*** Clinical advice suggests mild, moderate and severe hyperphagia appropriately reflect patient experience and methods of the vignette study appropriate, however: • Vignette study did not recruit POMC or LEPR patients • Utility loss associated with moving from moderate to severe hyperphagia (−0.484, 68.9% decrement) considerably higher than moving from mild to moderate (−0.207, 22.7% decrement). Company did not comment on reasonableness or attempt to validate values. ***Lack of robust data on hyperphagia a key uncertainty as not collected in trials.***

◉ *What is the committee view on the company's choice of utility values used in model?*

BMI, body mass index, SF-36, Short Form-36

Utilities, ERG comments (2)

Comorbidity and adverse events

- QoL impact may not be fully captured as AEs excluded from model, especially QoL impact for skin pigmentation (main AE in trials)
- Cancer not included in model due to short life expectancy in population, but plausible that setmelanotide responders have life expectancy long enough to develop cancer
- Comorbidity prevalence rates in model are:
  - equal for adults and children (except type 2 diabetes and CV events which only occur in adults). Osteoarthritis and NAFLD develop over time so likely low rates in children -> company may overestimate QoL impact of comorbidities
  - Based on general obesity - > not LEPR/POMC specific
  - Taken from different sources to those reported in HST14

ERG scenarios

1. Prevalence rates and disutilities for comorbidities decreased by 10%
2. Alternative hyperphagia utility multiplier based on those in HST14:

Hyperphagia	Disutility	Multiplier*	Source
Mild	-0.11	0.801	HST14 'presence of hyperphagia' utility (represents mild hyperphagia as ERG in HST14 considered utility low)
Moderate	-0.22	0.702	2x mild utility
Severe	-0.33	0.603	3 x mild utility value

* Assumes baseline utility of 0.9 (close to utility for BMI 25-30 in the 18-30 age group) as patients unlikely to be in full health at baseline. HST14 = Metreleptin for treating lipodystrophy. Source: ERG report, table 42

◉ *Which sources for utility values are preferred for decision making?*

AE, adverse event; BMI, body mass index; CV, cardiovascular; HST, highly specialised technology; NAFLD, non-alcoholic fatty liver disease; QoL, quality of life; SF-36, Short Form-36

Costs and resource use

Company's drug costs inputs

Company pools average dose from trials, ERG prefers separate doses by deficiency and age

Cost	Setmelanotide		Best supportive care	
	Cost (£)	Notes	Cost (£)	Notes
Technology	£2376/ 10mg	NHS list price without PAS	0	Included in obesity management costs
Administration	0	Self-administration	0	
Monitoring	66	Frequency: expert input. Costs: National Schedule of NHS costs, 2018-19, Unit Costs of Health and Social Care 2020	184	As setmelanotide
Total annual costs /patient	Year 1 [redacted] Year 2+ [redacted]	Average dose [redacted]mg/day in year 1 and [redacted] mg/day years 2+	0	Assumed negligible (physician visit costs included elsewhere)

ERG comments:

- Company pools adult & paediatric doses: small patient numbers in subpopulations
- Acknowledge small cohorts but ***approach inappropriate*** - > separate doses (and different costs) for adults & children used in the trials: would also be used in NHS
- Doses used in ERG base case:
  - POMC paediatric: [redacted] mg/day
  - POMC adult: [redacted] mg/day
  - LEPR paediatric: [redacted] mg/day
  - LEPR adult: [redacted] mg/day

Majority of costs accrued in setmelanotide arm are treatment costs: varying doses impacts ICER

- **ERG scenarios** using minimum and maximum doses according to the SmPC schedule also presented

Doses used in ERG scenarios

Years:	Dose (mg) 6 to < 12	Dose (mg) ≥ 12
Starting dose		
Min possible	0.5	1.0
Max possible	1.0	2.0
Dose after trial		
Min possible	2.0	2.0
Max possible	2.5	3.0

Source: ERG Appendix #2, table 2

◉ *What average dose should be used to calculate treatment costs in the model?*

Discount rate

Company uses a 1.5% discount rate for health benefits and 3.5% for costs; ERG prefers a 3.5% for both

NICE Methods Guide (published in ***2013***):

- Reference Case (and non-reference case) does not support use of differential discount rates

Interim HST methods guide *(2017), in line with 2013 NICE Methods Guide:*

  - A discount rate of 1.5% for ***costs and benefits*** may be considered *by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*

Company: Discount rate justified by:

- Responders to setmelanotide expected to have a comparable life expectancy to general obesity: considerable mortality benefit in base case; Significant QoL improvement due to hyperphagia reduction
- Differential discounting (1.5% for benefits, 3.5% for costs) accepted in TA235 (Mifamurtide for osteosarcoma, ***2011***). *NB: TA235 published before current NICE methods guide, 2013.*
- **ERG: *3.5% discount rate for both more appropriate*:** lack of robust long-term effectiveness and mortality data: company's LY and QALY gains modelled rather than evidenced - > ***considerable uncertainty and key model driver***

Clinical expert: expect improvements in BMI & hyperphagia but not complete/near symptom resolution

◉ *What is the committee's view on the discount rates that should be used in model?*

BMI, body mass index; HST, highly specialised technology; QoL, quality of life; TA, technology appraisal

Cost effectiveness estimates

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 (deterministic ICERs):

Deterministic analyses	Incremental QALYs - discounted	Incremental QALYs - undiscounted	ICER (PAS) (/QALY gained)
Company base case	[redacted]	[redacted]	**£141,550***
ERG preferred base case			
POMC paediatric population	[redacted]	[redacted]	**£218,390†**
POMC adult population	[redacted]	[redacted]	**£242,240†**
LEPR paediatric population	[redacted]	[redacted]	**£298,476†**
LEPR adult population	[redacted]	[redacted]	**£326,123†**
ERG scenarios			
Most optimistic QALY gain: Paediatric patients assumed to have 10% lower prevalence rates and disutility compared to adults in the POMC peadiatric population	[redacted]	[redacted]	**£155,082***
Most pessimistic QALY gain: 20-year time horizon in the LEPR paediatric population	[redacted]	[redacted]	**£213,239***

◉ *Can QALY weighting be applied to the company and ERG base cases?*

*costs discounted at 3.5%, benefits discounted at 1.5%. †Costs and benefits discounted at 3.5%. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

QALY, quality adjusted life year; QoL, quality of life

Company's base case

Company's deterministic and probabilistic base cases, setmelanotide + BSC vs. BSC, PAS for setmelanotide

	Total Costs	Total QALYs		Inc. costs	Inc. QALYs		ICER*
		Discounted*	Undiscounted		Discounted*	Undiscounted	
Company deterministic base case in the overall population (weighted average)†							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£141,550**
BSC	£30,451	3.94	4.53	-	-		-
Company probabilistic base case in the overall population (weighted average) †							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£142,191**
BSC	£30,388	3.95	4.57	-	-		-

*1.5% for health benefits, 3.5% for costs. Undiscounted QALYs calculated by the ERG.

†weighted average by proportion of deficiencies reported in the literature. Source: ERG appendix, table 2

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Company's scenario analyses, including PAS

Company's deterministic scenario analyses, setmelanotide vs. standard care, PAS for setmelanotide

Scenario	ICER*	Δ from base case	% change
Company base case	**£141,550**	-	-
Population			
Uniform baseline BMI distribution	**£139,095**	-£2,455	-2
Distribution of POMC and LEPR based on trial population	**£143,990**	+£2,440	+2
Distribution of children and adults based on trial population	**£143,018**	+£1,468	+1
Treatment effect			
All responders have 1 level of improvement in hyperphagia	**£153,471**	+£11,921	+8
Response rate stratified by age group based on trial	**£141,631**	+£81	+0
Hyperphagia mapping based on worst hunger score	**£179,686**	+£38,136	+27
Costs			
Incremental cost of BSC by BMI	**£141,362**	-£188	-0
Account for acute costs of CV events	**£141,567**	+£17	+0
Comorbidities and utilities			
Increased co-morbidity disutility by 50%	**£141,728**	+£178	+0
Inclusion of only co-morbidities prevalent in children	**£141,369**	-£181	-0
Utility scores decreased by 0.05 for BMI ≥ 50	**£141,386**	-£164	-0

**1.5% for health benefits, 3.5% for costs. Weighted average by proportion of deficiencies reported in literature.*

BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

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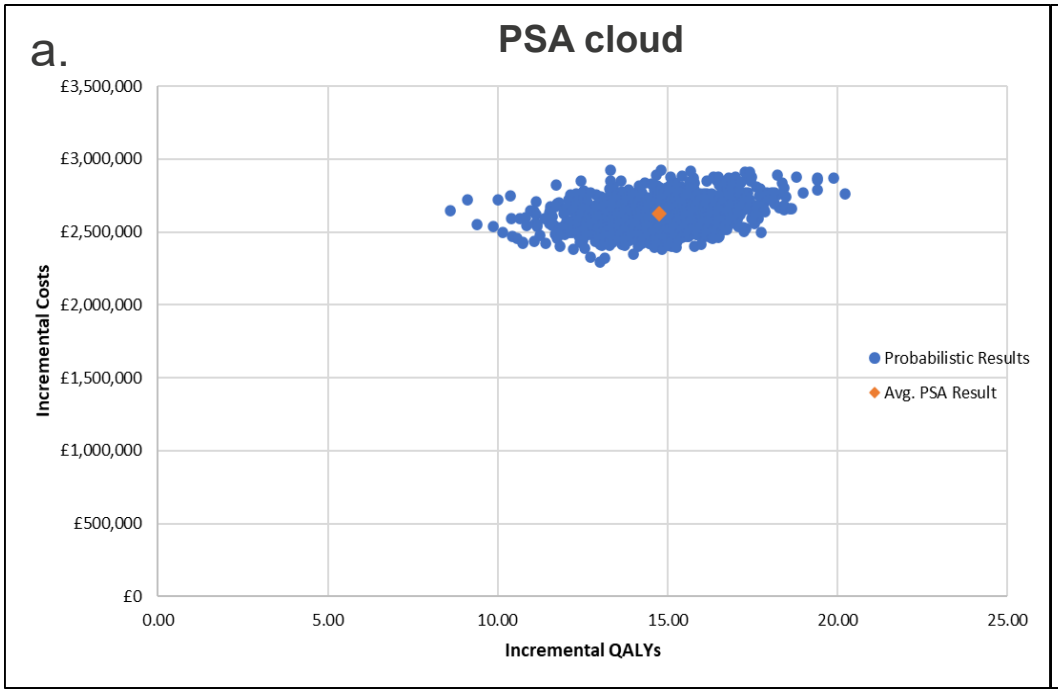
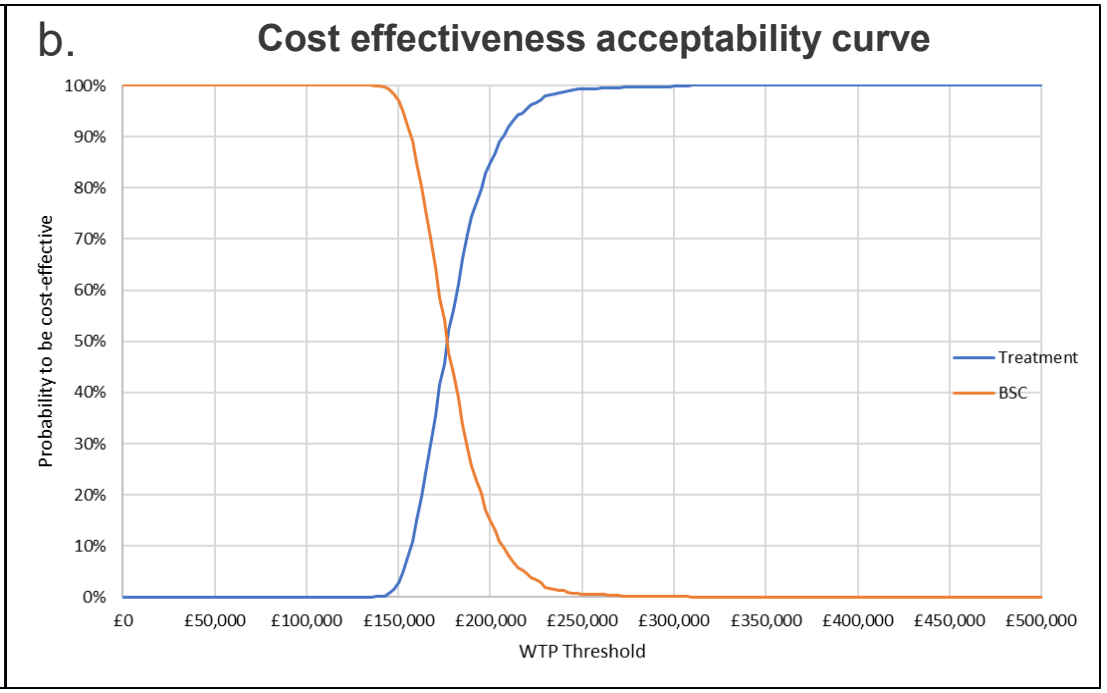
Source: ERG confidential appendix, table 3

Company's probabilistic sensitivity analyses

Company's probabilistic sensitivity analyses, a) PSA cloud, b) cost effectiveness acceptability curve, setmelanotide versus BSC, replicated by ERG with PAS price for setmelanotide





Source: ERG report, figures 3 and 4

Deterministic sensitivity analyses

Most influential parameters:

- Variation in discount rate for costs (0% and 1.5%) and benefits (0% and 3.5%)
- Reduced time horizon (10 years, 20 years)
- Setmelanotide dose after the trial duration (1.5 mg/day, 2.2 mg/day)
- Hyperphagia utility multiplier (+/- 10%)

NB: ICER remains above £100,000/QALY gained in all scenarios

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis, QALYs, quality-adjusted life years

Shared assumptions in company & ERG base cases

Assumptions	Description
Model structure	• Markov state-transition model based on BMI/BMI-Z score
Baseline population	• Proportion of adults & children: Argente et al. 2019 • Distribution of deficiency type: Graves et al. 2021
Treatment effectiveness	• Trial period: results on BMI gain at 52-week, pivotal trials • Post trial: based on clinical expert opinion
Response to treatment	• Trial period: response in RM-493-12 and -15 at 12 weeks (equal to rates at 52 weeks) • Post trial: overall response rates across BMI classes and BMI Z-scores, averaged for adults and children
Hyperphagia	• Baseline severity distribution: UK clinical expert's opinion • Treatment effect: average change in daily worst hunger scores at 52 weeks mapped to hyperphagia severity
Mortality for responders	• Clinical opinion that life expectancy similar to people with general obesity of similar BMI level
HRQoL/utilities	• BMI: EQ-5D utilities from literature on general obesity population (adults and children) • Hyperphagia utility multiplier: from vignette study • Disutility associated with comorbidities: from literature

NICE

BMI, body mass index

Differing assumptions in company & ERG base cases

Discount rate drives the difference between company & ERG base cases

Assumption	Company base case	ERG base case	Impact
Population	Overall population using pooled data from pivotal trials, no separation by deficiency or age	4 separate subgroups: • POMC children • POMC adult • LEPR children • LEPR adult	
Setmelanotide dose	Average dose from clinical trials using pooled adult and paediatric data	Average dose from clinical trials using separate adult and paediatric data	
Mortality rate for non-responders & best supportive care	Clinical expert opinion for mean and max life expectancy	Life expectancy converted to equivalent HR multiplier	
Stopping treatment	No stopping treatment modelled	1% stop treatment throughout lifetime as based on TA664	
Discount rate	1.5% for health benefits, 3.5% for costs	3.5% for both health outcomes and costs	

 Model driver: >£50,000 per QALY gain change from base case;

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

 Moderate impact: <10,000 per QALY gained change from base case

ERG's base case analyses, POMC patients

ERG base cases, setmelanotide + BSC vs. BSC, PAS for setmelanotide

	Total Costs	Total QALYs		Inc. costs	Inc. QALYs		ICER*
		Discounted*	Undiscounted		Discounted*	Undiscounted	
POMC, paediatric population							
Deterministic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£218,390†**
BSC	£41,504	4.85	8.54	-	-	-	-
Probabilistic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£218,878†**
BSC	£41,602	4.84	8.51	-	-	-	-
POMC, adult population							
Deterministic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£242,240**
BSC	£38,619	3.87	6.09	-	-	-	-
Probabilistic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£242,966**
BSC	£41,602	4.84	6.07	-	-	-	-

**Costs and benefits discounted at 3.5%. † denotes results under the cost effectiveness threshold when applying QALY weighting.* Source: ERG report appendix, tables 4 and 5

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

ERG's cumulative changes: POMC patients

ERG cumulative base cases, setmelanotide + BSC vs. BSC, PAS for setmelanotide

	Children				Adults			
Scenario	**Inc. cost***	**Inc. QALYs**		**ICER***	**Inc. cost***	**Inc. QALYs**		**ICER***
		Undiscounted	**Discounted**			**Undiscounted**	**Discounted**	
Company's base case	[redacted]	[redacted]	[redacted]	**£152,938**	[redacted]	[redacted]	[redacted]	**£146,381**
ERG corrected company base case								
Hyperphagia treatment effect applied at end of 1st cycle rather than start	[redacted]	[redacted]	[redacted]	**£154,265**	[redacted]	[redacted]	[redacted]	**£147,713**
ERG's preferred base case								
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	**£127,919**	[redacted]	[redacted]	[redacted]	**£143,156**
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	**£133,300**	[redacted]	[redacted]	[redacted]	**£145,344**
Non-responder & BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	**£131,054**	[redacted]	[redacted]	[redacted]	**£150,498**
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£218,390**	[redacted]	[redacted]	[redacted]	**£242,240**

*costs discounted at 3.5%, benefits discounted at 1.5% unless specified. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

ERG's scenario analyses, POMC patients

ERG's deterministic scenario analyses with ≥5% change on base case, setmelanotide vs. BSC, PAS for setmelanotide

	Children		Adults	
	ICER £/QALY*	Δ from base case	ICER £/QALY*	Δ from base case
ERG corrected company base-case	**£154,265**	-	**£147,713**	-
Modelled treatment effectiveness				
BMI regain after trial period	**£196,679**	27%	**£189,988**	29%
Alternative hyperphagia baseline distribution + transition probability from HST14	**£244,166**	58%	**£202,411**	37%
Mortality				
No mortality benefit for responders	**£195,000**	26%	**£196,499**	33%
10% decrease in company's mortality multiplier for non-responders and BSC	**£155,263**	1%	**£155,174**	5%
Applying the dosing schedule in the SmPC				
Minimum possible dose both at start and after trial	**£168,847**	9%	**£161,523**	9%
Maximum possible dose both at start and after trial	**£254,537**	65%	**£243,455**	65%
Other				
Separate dosing for children & adults	**£127,919**	-17%	**£143,156**	-3%
3.5% discount rate for health	**£270,333**	75%	**£243,013**	65%
20-year time horizon	**£259,792**	68%	**£230,195**	56%

*costs discounted at 3.5%, benefits discounted at 1.5% unless specified. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years; SmPC, summary of product characteristics. Source: ERG report appendix, tables 4 and 5

ERG's base case analyses, LEPR patients

ERG's base cases, setmelanotide + BSC vs. BSC, PAS for setmelanotide

	Total Costs*	Total QALYs		Inc. costs*	Inc. QALYs		ICER*
		Discounted	Undiscounted		Discounted	Undiscounted	
LEPR, paediatric population							
Deterministic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£298,476**
BSC	£27,166	2.51	3.63	-	-	-	-
Probabilistic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£301,661**
BSC	£27,202	2.52	3.63	-	-	-	-
LEPR, adult population							
Deterministic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£326,123**
BSC	£21,396	1.22	1.54	-	-	-	-
Probabilistic base case							
Setmelanotide + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£329,080**
BSC	£21,413	1.22	1.53	-	-	-	-

*Costs and benefits discounted at 3.5%. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. Source: ERG report appendix, tables 4 and 5

ERG's cumulative changes: LEPR patients

ERG's cumulative base cases, setmelanotide + BSC vs. BSC, PAS for setmelanotide

	Children				Adults			
Scenario	**Inc. cost***	**Inc. QALYs**		**ICER***	**Inc. cost***	**Inc. QALYs**		**ICER***
		Undiscounted	**Discounted**			**Undiscounted**	**Discounted**	
Company's base case	[redacted]	[redacted]	[redacted]	**£132,392**	[redacted]	[redacted]	[redacted]	**£145,738**
ERG corrected company base case								
Hyperphagia treatment effect applied at end of the 1st cycle rather than start	[redacted]	[redacted]	[redacted]	£133,528	[redacted]	[redacted]	[redacted]	£147,245
ERG's preferred base case								
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	£172,290	[redacted]	[redacted]	[redacted]	£203,012
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	£186,782	[redacted]	[redacted]	[redacted]	£206,084
Non-responder and BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	£184,443	[redacted]	[redacted]	[redacted]	£209,440
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£298,476**	[redacted]	[redacted]	[redacted]	**£326,123**

*costs discounted at 3.5%, benefits discounted at 1.5% unless specified. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

ERG's scenario analyses, LEPR patients

ERG's deterministic scenario analyses with ≥5% change on base case, setmelanotide vs. BSC, PAS for setmelanotide

	Children		Adults	
	ICER £/QALY*	Δ from base case	**ICER £/QALY***	Δ from base case
ERG corrected company base-case	**£133,528**	-	**£147,245**	-
Modelled treatment effectiveness				
BMI regain after trial period	**£154,265**	16%	**£147,713**	0%
[redacted]BMI [redacted] for LEPR during trial period	**£139,594**	5%	**£153,408**	4%
Alternative hyperphagia baseline distribution, HST14 transition probability	**£172,498**	29%	**£172,789**	17%
1% discontinuation rate	**£144,810**	8%	**£149,513**	2%
Mortality				
No mortality benefit for responders	**£176,297**	32%	**£198,546**	35%
↑ mean & max age life expectancy: non-responders & BSC	**£153,172**	15%	**£166,731**	13%
Applying the dosing schedule in the SmPC				
Minimum possible dose both at start and after trial	**£145,560**	9%	**£160,115**	9%
Maximum possible dose both at start and after trial	**£219,166**	64%	**£240,502**	63%
Other				
Separate dosing for children and adults	**£172,290**	29%	**£203,012**	38%
3.5% discount rate for health	**£232,090**	74%	**£233,697**	59%
20-year time horizon	**£213,239**	60%	**£191,987**	30%

*costs discounted at 3.5%, benefits discounted at 1.5% unless specified. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years; SmPC, summary of product characteristics. Source: ERG report appendix, tables 10 and 11

Other considerations

Service design and delivery

Unclear where setmelanotide would be administered in the NHS

Company: Setmelanotide would be given in all tier 3 centres plus planned network of 14 commissioned paediatric centres

Current Tier 3 service provision

- Commissioned at a local level: can be in primary or secondary care
- Variation in access to tier 3 services noted in ***NHS England's report on joined up clinical pathways for obesity (2014)*** and ***TA664***: *The provision of tier 3 services is variable, with the absence of such services in many areas.*

Clinical experts: Only in tertiary care specialist clinics with shared care and secondary care clinicians. Additional requirements:

- Specialist monitoring of disease processes: limited patient numbers so specialists key to ensure appropriate use.
- Training for specialist clinicians on technology and scope of conditions, including dose titration and monitoring.
- Patients or carers need to be taught to self-administer daily injections

NHS England:

- Administered through national centre of excellence only
- Genetic testing required to confirm diagnosis, but no additional investment required

Equalities

Population includes children; self-administration by injection may require additional support

Setmelanotide is indicated for use in children (aged 6 years of age and above) and adults.

Company and ERG: did not identify any equality issues for setmelanotide.

Clinical and patient experts:

- Biallelic, recessive disorders disproportionately affect people from ethnic backgrounds where consanguineous marriage more commonly practised.
- Setmelanotide injectable so people with vision problems, learning difficulties, physical disability and needle phobia need support: should already be in place to manage other health needs.
- Patients need access to tertiary clinicians and transport to secondary or tertiary units for monitoring and screening.

◉ *Are there any potential equalities issues that should be considered for setmelanotide?*

Innovation

Company and clinical experts state innovative for LEPR/POMC obesity population

Company:

- Only pharmacotherapy indicated for chronic weight management that treats underlying cause of the conditions and hyperphagia
- Patients currently endure ineffective treatments, such as diet and exercise advice. Stigma attached to being obese and inability to control eating habits.
- Shown in clinical trials to reduce hyperphagia and lead to substantial weight loss, significant impact on physical and mental health.

Clinical experts: '*transformative for the care of patients with these rare disorders'*

- *Clinically effective:* Weight loss in trials substantially larger than with other therapies.
  - Targeted towards mechanism causing the obesity
- *Addresses unmet need in population*:
  - No targeted treatment currently available, many patients die of the disease.
  - Lifestyle changes with severe permanent restrictions on food intake very difficult to sustain.
- *Likely significantly improves quality of life:* improves mobility and comorbidities, but also confidence and self-esteem, reduces stigma and increases engagement with education and employment (which may not be fully captured in QALYs)

◉ *Does setmelanotide represent a step change in treatment?*

QALY, quality-adjusted life year

Managed Access

- The MAA team consider the following sources are currently feasible to collect within an MAA:
  - Further data, including quality of life, from RM-493-022 extension study due to complete March 2023
  - Proportion of LEPR and POMC and dosage used in clinical practice
- No existing data source currently collects relevant outcome data in clinical practice
- Any bespoke data collection arrangement to collect key model outcomes, i.e. BMI and hyperphagia, in clinical practice may not be feasible or proportionate to the clinical uncertainties. This would require time to explore, design and implement.
- The MAA team highlight the following additional considerations:
  - Further data collection would not provide meaningful data on mortality
  - RM-493-022 conducted in Germany. No patients in trial received setmelanotide at the anticipated UK dose of 3.0mg

Key issues, clinical effectiveness

Treatment pathway	*Company positions setmelanotide as 1st line treatment for LEPR/POMC obesity.* • How are LEPR and POMC deficiencies currently diagnosed? • What treatment do people with LEPR and POMC obesity currently have? • What is the committee's view of the proposed positioning of setmelanotide?
Population	*Clinical trials are small with strict exclusion criteria and few UK patients* • Are results generalisable to the population in the NHS?
Intervention	*Clinical trials recruited people from countries with different dosing schedules than licenced in UK* • What is the committee's view on dosing differences between the trials and marketing authorisation? How does this impact their generalisability to NHS practice?
Comparator/ comparative effectiveness	*Company excludes orlistat, methylcellulose and bariatric surgery as comparators* • What is the committee's view of excluding these comparators?
	There is no direct clinical evidence on the modelled comparator, standard management • Can committee judge the treatment effect of setmelanotide relative to best supportive care?
Clinical effectiveness	*Clinical evidence comes from small single-arm studies* • What is the committee view on setmelanotide's treatment effect on: body weight loss; reduction in BMI; hunger, and quality of life?
	Clinical trials exclude several scoped outcomes • What is committee's view on the absence of clinical evidence on setmelanotide's treatment effect on: mortality; hyperphagia (assessed indirectly through hunger scores only); and other outcomes listed in the NICE scope?
	Short total treatment duration (52 weeks) but extension study results suggest a plateau of effect • What is the committee's view on the long-term treatment effect of setmelanotide? • Do results suggest a waning of treatment effect?
	Differences in treatment effect observed for people by deficiency type • Should subgroups be considered separately based on deficiency type?

Key issues, cost effectiveness

Model structure	*Company's model structure uses BMI health states and death. What is the committee's view on:* • The company's general model structure? • The modelling of BMI cut-offs and hyperphagia status as a condition within BMI health states? Is the company's model appropriate for decision making?
Population & subgroups	*The company uses the overall population for its cost-effectiveness analyses* • Are subgroup analyses based on age and/or deficiency type more appropriate for decision making?
Long term treatment effect	*The company' uses clinical expert opinion to inform long-term treatment effect and assumed no waning* • Would setmelanotide's effect on BMI and hyperphagia be maintained in long term?
Hyperphagia	*The company models a reduction in hyperphagia in setmelanotide responders* • What proportion of the population would have severe, moderate and mild hyperphagia at baseline? • What level of hyperphagia reduction is expected in responders to setmelanotide? • Should hyperphagia utility modifiers come from the company's vignette study or previous HST?
Mortality	*The company uses clinical expert opinion to predict life expectancy for setmelanotide non-responders and BSC, but general obesity mortality rates for responders* • Are these assumptions plausible? Has mortality been modelled correctly
Stopping treatment	*The company does not include stopping treatment in model* • Would people discontinue setmelanotide for reasons other than loss of response? If yes, at what rate?
Cost/dosing	*The company pools average adult and paediatric doses from trials to calculate treatment costs* • Should separate doses be used for adults and children in model?
Discounting	*The company uses a discount rate of 1.5% for benefits in its base case.* • Is this assumption appropriate, or should a discount rate of 3.5% be used?
QALY weighting	*Company and ERG base cases suggest significant QALY gains for setmelanotide compared with BSC* • Can QALY weighting be applied for this topic?

BMI, body mass index; BSC, best supportive care; HST, highly specialised technology; QALY, quality adjusted life year

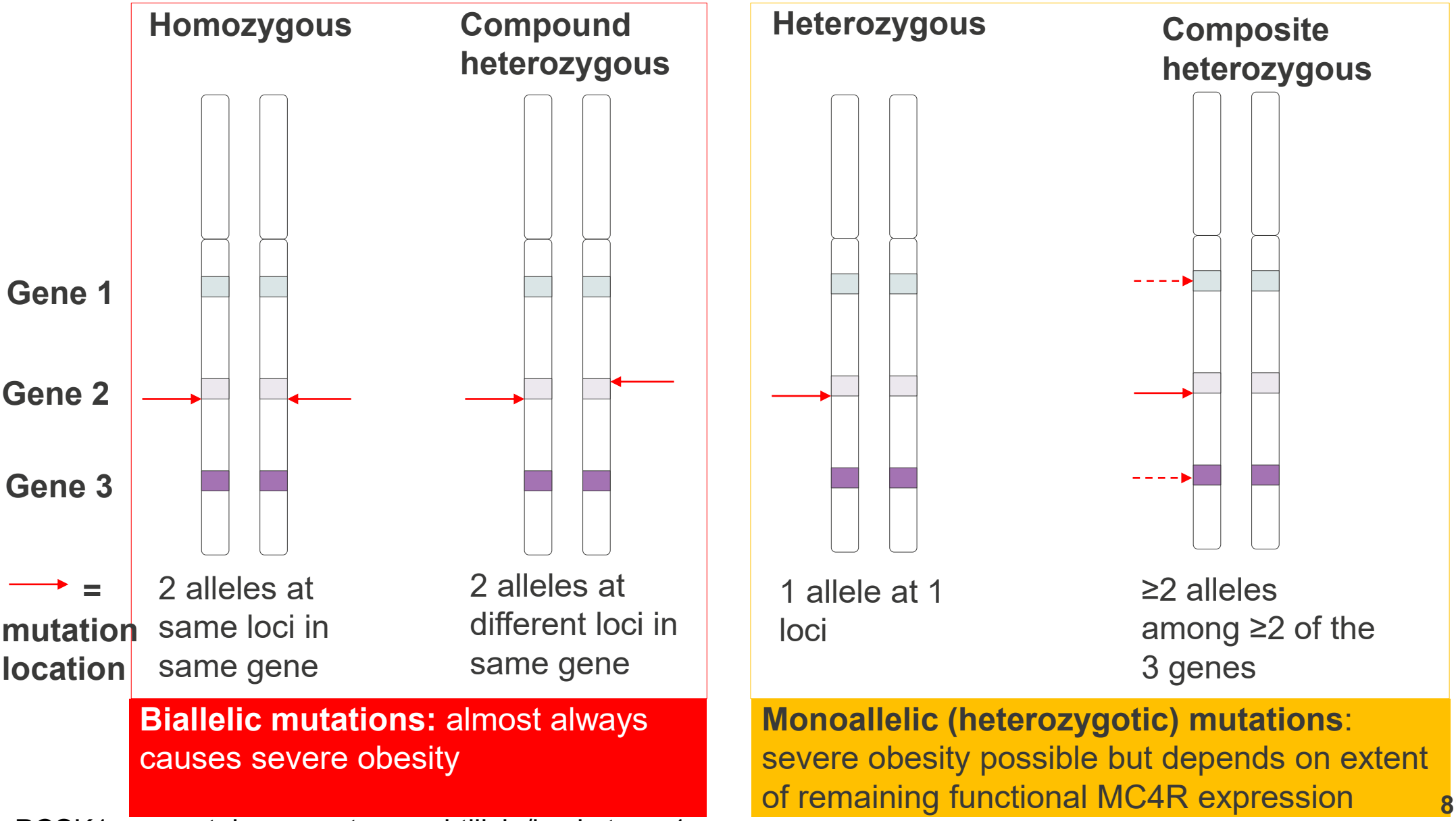
Back-up slides

Possible mutations in LEPR, POMC and PCSK1

Severe obesity likely for biallelic mutations but possible for monoallelic mutations

4 different types of mutation possible in each of the 3 genes of interest (LEPR, POMC including PCSK1)

Examples of different possible mutations affecting 'Gene 2':



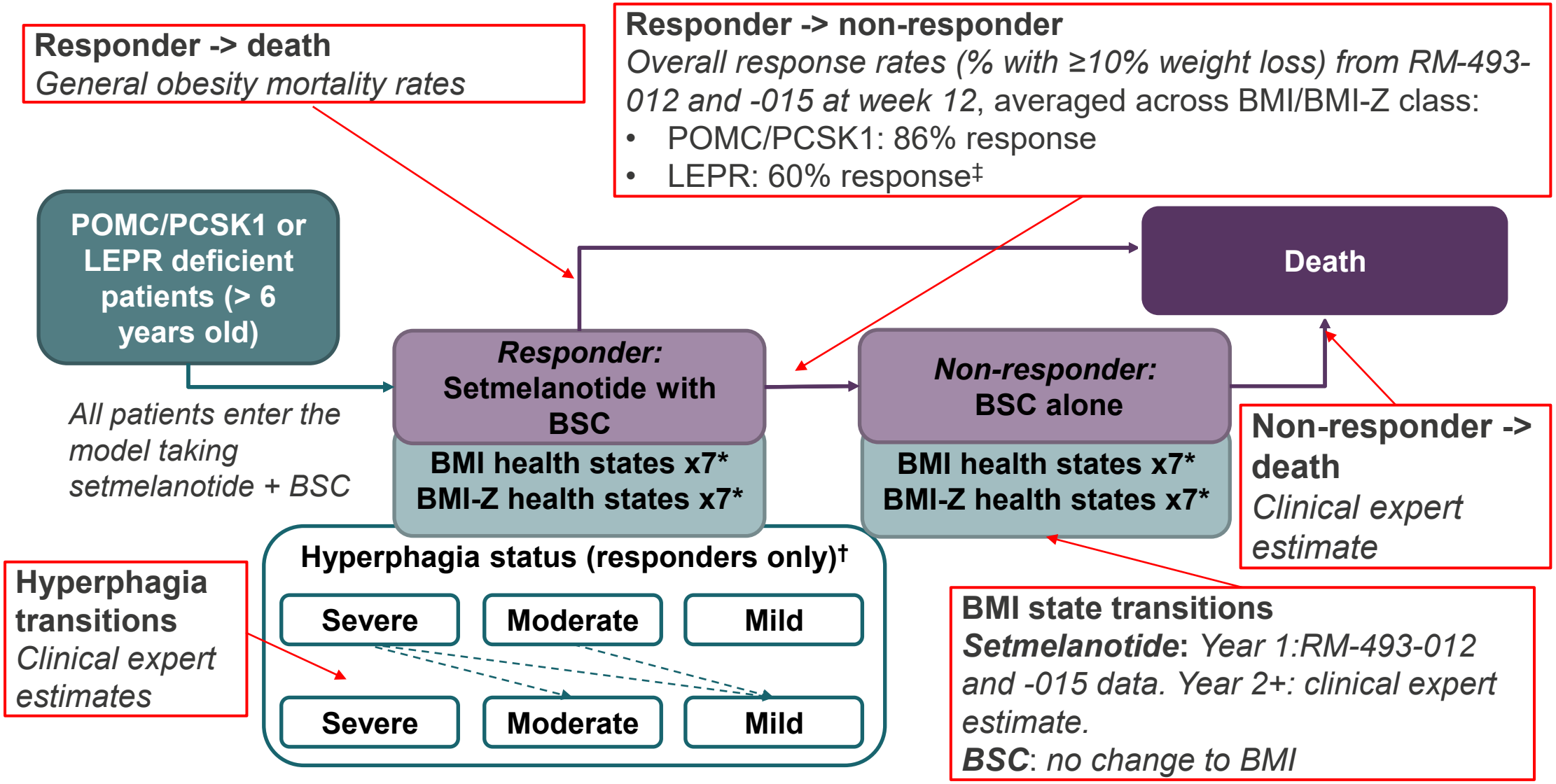
Biallelic mutations: almost always causes severe obesity

Monoallelic (heterozygotic) mutations: severe obesity possible but depends on extent of remaining functional MC4R expression

PCSK1, proprotein convertase-subtilisin/kexin type-1;

Data informing the health state transitions

Little clinical data to inform transition probabilities: predominantly based on expert opinion



**Direct cost and utility also linked to each BMI health state for obesity related comorbidities (all patients)*

† Hyperphagia status applied at the start of cycle 1 and persists throughout a patients lifetime whilst on treatment

‡ LEPR response rate in trial = 53%. Higher rate includes extra patient who responded clinically but didn't meet weight loss endpoint

Company's scenario analyses, including PAS

Company's deterministic scenario analyses, setmelanotide vs. standard care, PAS for setmelanotide

Scenario	Incremental QALYs		ICER	Δ from base case	% change
	Discounted	Undiscounted			
Company base case			**£141,550**	-	-
Population					
Uniform baseline BMI distribution	[redacted]	Not available	**£139,095**	-£2,455	-2
Distribution of POMC and LEPR based on trial population	[redacted]		**£143,990**	+£2,440	+2
Distribution of children and adults based on trial population	[redacted]		**£143,018**	+£1,468	+1
Treatment effect					
All responders have 1 level of improvement in hyperphagia	[redacted]	Not available	**£153,471**	+£11,921	+8
Response rate stratified by age group based on trial	[redacted]	[redacted]	**£141,631**	+£81	+0
Hyperphagia mapping based on worst hunger score	[redacted]	Not available	**£179,686**	+£38,136	+27
Costs					
Incremental cost of BSC by BMI	[redacted]	[redacted]	**£141,362**	-£188	-0
Account for acute costs of CV events	[redacted]	Not available	**£141,567**	+£17	+0
Comorbidities and utilities					
Increased co-morbidity disutility by 50%	[redacted]	[redacted]	**£141,728**	+£178	+0
Inclusion of only co-morbidities prevalent in children	[redacted]	[redacted]	**£141,369**	-£181	-0
Utility scores decreased by 0.05 for BMI ≥ 50	[redacted]	[redacted]	**£141,386**	-£164	-0

BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Source: ERG confidential appendix, table 3

ERG's scenario analyses, POMC patients

ERG's deterministic scenario analyses with ≥5% change on base case, setmelanotide vs. BSC, PAS for setmelanotide

	Children			Adults		
	Undiscounted QALYS	ICER* £/QALY	Δ from base case	Undiscounted QALYS	ICER* £/QALY	Δ from base case
ERG corrected company base-case	[redacted]	**£154,265†**	-	[redacted]	**£147,713†**	-
Modelled treatment effectiveness						
BMI regain after trial period	[redacted]	**£196,679**	27%	[redacted]	**£189,988**	29%
Alternative hyperphagia baseline distribution + transition probability from HST14	[redacted]	**£244,166**	58%	[redacted]	**£202,411**	37%
Mortality						
No mortality benefit for responders	[redacted]	**£195,000†**	26%	[redacted]	**£196,499†**	33%
10% decrease in company's mortality multiplier for non-responders and BSC	[redacted]	**£155,263†**	1%	[redacted]	**£155,174†**	5%
Other						
Separate dosing for children & adults	[redacted]	**£127,919†**	-17%	[redacted]	**£143,156†**	-3%
3.5% discount rate for health	[redacted]	**£270,333†**	75%	[redacted]	**£243,013†**	65%
20-year time horizon	[redacted]	**£259,792**	68%	[redacted]	**£230,195**	56%

*Costs and benefits discounted at 3.5%. **† denotes results under the cost effectiveness threshold when applying QALY weighting.** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. Source: ERG report appendix, tables 4 and 5

ERG's scenario analyses, LEPR patients

ERG's deterministic scenario analyses with ≥5% change on base case, setmelanotide vs. BSC, PAS for setmelanotide

	Children			Adults		
	Undiscounted QALYS	ICER £/QALY	Δ from base case	Undiscounted QALYS	**ICER £/QALY**	Δ from base case
ERG corrected company base-case	[redacted]	**£133,528†**	-	[redacted]	**£147,245†**	-
Modelled treatment effectiveness						
BMI regain after trial period	[redacted]	**£154,265**	16%	[redacted]	**£147,713**	0%
[redacted]BMI drop for LEPR during trial period	[redacted]	**£139,594**	5%	[redacted]	**£153,408**	4%
Alternative hyperphagia baseline distribution, HST14 transition probability	[redacted]	**£172,498**	29%	[redacted]	**£172,789**	17%
1% discontinuation rate	[redacted]	**£144,810**	8%	[redacted]	**£149,513**	2%
Mortality						
No mortality benefit for responders	[redacted]	**£176,297†**	32%	[redacted]	**£198,546†**	35%
↑ mean and max age life expectancy: non-responders & BSC	[redacted]	**£153,172†**	15%	[redacted]	**£166,731†**	13%
Other						
Separate dosing for children and adults	[redacted]	**£172,290†**	29%	[redacted]	**£203,012†**	38%
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20-year time horizon	[redacted]	**£213,239**	60%	[redacted]	**£191,987**	30%

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