Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (review of HST31) [ID6598]

For ONSCREEN – contains redacted information

Technology appraisal rare disease committee ID6598 as a Highly Specialised

Technology appraisal 25 June 2026

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Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (review of HST31) [ID6598]

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background: HST31 recap

Main conclusions/considerations & remained uncertainty	

Population	• **Was considered for both children (from age 6) and adults**
	  ○ **Subset recommended:** starting at age 6 to 17 years → greater benefits
	  ○ Starting in adults not recommended (proportionate to NICE's legitimate aim to recommend clinical- and cost-effective technologies)

Treatment effect	• Setmelanotide likely improves obesity-related (weight loss and BMI) and other outcomes (hunger, metabolic and QoL) in the short term in BBS; • Lack of trial evidence on setmelanotide's treatment effect on hyperphagia
Major uncertainty	• Defining and classifying hyperphagia severity, baseline distribution in model • Long term treatment effect in obesity reduction and hunger • Treatment stopping • Costs and utilities of obesity-related comorbidities • QoL impact: of non-obesity-related comorbidities (visual impairment and learning difficulties); and for people with BBS and their carers
Weighting	• 90% QALY weight applied due to high uncertainty in robustness of QALYs
Equality	All equalities issues for setmelanotide had been considered in its decision making (Equality considerations summarised in later slides)

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body-mass index; QALY, quality-adjusted life years; QoL, quality of life

Background: what has changed since HST31, main additional evidence

Current review considers **starting treatment in adults**, and

- whether additional evidence since HST31 sufficiently reduces uncertainty and improves the clinical- and cost-effectiveness for starting treatment in adults

Area	Main new evidence
Clinical effectiveness for weight outcomes	• Setmelanotide arm from RM-493-023, including adult subgroup, compared with simulated external matched control arm (CRIBBS database; Argente et al. 2025) up to 52 weeks – informs BMI/BMI-z shifts in model
	• Updated RM-493-022 LTE single arm follow-up (up to 5 years)
Hyperphagia / severity / QoL	• UK HSinBBS study (Mossman et al. 2026), questionnaire and interviews informing hyperphagia severity distribution at baseline (only)
	• Qualitative interviews on hunger and hyperphagia (Ervin et al. 2023), and survey on hunger and weight (Finkelberg et al. 2025), in patients and carers
	• 2 prospective, single-arm RWE cohort studies (Germany: Hühne et al. 2025, France: Mifsud et al. 2025), hyperphagia improvement using questionnaires, hunger and related eating behaviour
Other	• Hühne et al. 2025, potential MASLD/kidney benefits beyond BMI reduction
Model	• Co-base case in whole-population: informs QALY weighting and ICER

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body-mass index; CRIBBS, Clinical Registry Investigating BBS; LTE, long-term extension; MASLD, metabolic dysfunction-associated steatotic liver disease; QALY, quality-adjusted life years; QoL, quality of life; RWE, real world evidence

Background: Bardet-Biedl syndrome

Rare genetic disorder of hyperphagia (extreme, insatiable hunger) and obesity

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

Mutations in one or more of the BBS associated genes leading to disrupted MC4R signalling → Dysregulated hunger, satiety and energy expenditure → Key features (see Appendix for BBS symptoms):

1. early onset, severe obesity, and
2. hyperphagia: overwhelming, heightened & relentless hunger with feelings of starvation, longer time to reach satiety, lasts shorter time

- **Epidemiology:** prevalence estimated at about 1 per 100,000 people in the UK
- **Obesity-related complications:** reduced mobility, T2D, hypertension, psychological
- **Quality of life:** large impact and multiple comorbidities. Obesity and hyperphagia key factors; depression, social isolation and stigma; vision loss can limit daily activities
- **Prognosis:** lack of evidence on life expectancy: renal failure and obesity related comorbidities thought to be major causes of death

Abbreviations: BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4-receptor; QoL, quality of life; T2D, type 2 diabetes

Patient perspectives (1/2)

Impact of BBS on the individual with the condition and their family is profound

Submissions from patient experts and Bardet-Biedl Syndrome UK

- Hyperphagia and obesity experienced alongside visual impairment, learning disability and emotional dysregulation, meaning individuals face simultaneous cognitive, physical and behavioural challenges
- Eating behaviours may become highly structured or ritualised, significant mental energy devoted to planning, budgeting or restricting access to food
- High levels of anxiety among people living with BBS and their carers

Adults describe constant internal food noise, persistent thoughts about future meals, and difficulty concentrating on work or daily tasks when hungry… including waking at night with hunger… makes me feel anxious and exhausted

Abbreviations: BBS, Bardet-Biedl syndrome

Patient perspectives (2/2)

Unmet need within existing services and treatments for adults with BBS

- Significant carer burden: 70% of adults with BBS continue to live within family home, reflecting the condition's significant impact on independence
- Many barriers to accessing treatment including waiting times and eligibility criteria
- Access to specialised BBS clinics and multidisciplinary management highly valued. But no NHS commissioning of treatment for hyperphagia in adults
- Weight-management programmes and lifestyle interventions support general health, but very difficult to sustain in context of persistent hunger

> I feel constantly judged… very conscious about what other people are thinking and very self-conscious about my weight and what I am eating. But losing weight is much harder because the hunger and food noise are always there

Abbreviations: BBS, Bardet-Biedl syndrome

Clinical perspectives (1/2)

Adults with BBS experience debilitating hyperphagia and obsessive food noise

Expert submissions (further input is on other slides)

- For adults, burden of BBS intense and often evolves… continue to experience debilitating hyperphagia and obsessive food noise, compounded by vision impairment, potential renal complications, reduced mobility, and challenges with independence and mental health
- Treatment of BBS aims to reduce cardiovascular risk and impact of obesity related disease, improve function and quality of life, and reduce impact of hunger and hyperphagia
- Weight loss maintenance or weight stability is a clinically relevant treatment response → likely to impact survival

Families report high levels of emotional distress, social isolation, constant supervision around food, and weight challenges

BBS is fundamentally different from the hunger or cravings seen in common obesity, where lifestyle interventions can often be more effective

Abbreviations: BBS, Bardet-Biedl syndrome

Clinical perspectives (2/2)

Setmelanotide allows targeted treatment of BBS through MC4R pathway

- Adults: No licensed, effective pharmacological treatments specifically for the hyperphagia and obesity in BBS → missed opportunity to improve outcomes in a rare disease
- Standard of care (diet and exercise) largely ineffective against the underlying MC4R pathway dysfunction
- Setmelanotide is absolutely innovative → allows targeted treatment of BBS as opposed to the use of treatment of obesity for the whole population living with obesity
- Care highly specialised, delivered through adult BBS clinics
- UK centre included in key setmelanotide trial

Setmelanotide: real-world evidence and patient reports highlight reductions in obsessive food noise and food-seeking behaviours → broader improvements in quality of life, functioning, mental health, and family dynamics

Abbreviations: BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4-receptor

Key issues for discussion

	Key issue	ICER impact
Decision problem	Population for decision problem	Large (population) Small (adult age)
	Relevance of GLP-1 receptor agonists for adults living with BBS obesity and hyperphagia	Unknown
Model	Distribution of hyperphagia at baseline for adults	Large
	Estimation of BMI and BMIz class shifts	Moderate
	Potential additional effect of setmelanotide on MASH beyond effect on MASH due to change in BMI	Moderate
	Potential additional effect of setmelanotide on kidney disease beyond effect on kidney disease due to change in BMI	Moderate
	Setmelanotide treatment discontinuation rate	Small (adults) Large (whole population)
	Disutility due to non-obesity related BBS symptoms	Large

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis

Other issues for discussion

Other issue	ICER impact
Evidence source for impact of BMI on utilities in children	Small (whole population only)
Application of QALY weight in probabilistic results	Moderate
Potential inequity concern due to the age restriction on initiation of setmelanotide in HST31	N/A – Equalities

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body-mass index; QALY, quality-adjusted life years

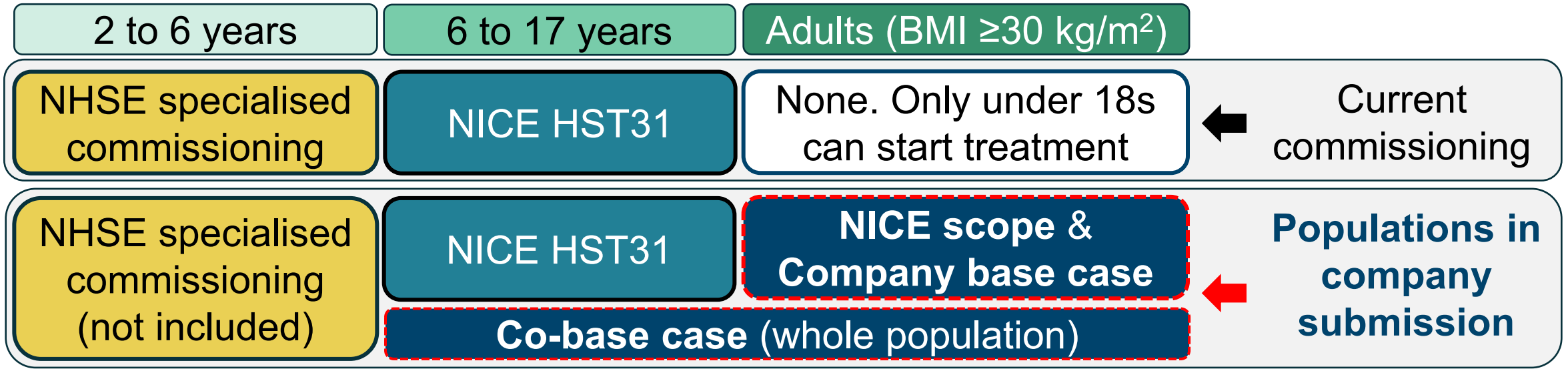
Populations in company submission

Company: people starting treatment as adults & whole population (6 years to adult)

Background

- Company's original population in HST31 was paediatric and adult initiators
  - Optimised recommendation in a subpopulation with greater benefits – people starting treatment aged 6 to 17 years
- Population in NICE scope for this review: 'Adults with obesity and hyperphagia in BBS'

Age starting* setmelanotide for BBS: (*treatment can continue into adulthood)



Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Key issue: Population for decision problem (1/2)

Company: whole population gives context to adult population

Background

- HST31 recommended starting setmelanotide in people with BBS aged 6 to 17 years → greater benefit and proportionate to NICE's legitimate aims
- Unmet need remains for people potentially starting treatment aged 18 years or older

Company – base case population is adults, whole population gives context

- Evaluation in HST31 was for whole population, but an optimised recommendation made
- Since HST31, new evidence has clarified the broader clinical burden of BBS and strengthened understanding of MC4R pathway dysfunction for people living with BBS
- Post hoc analyses of key studies done and RWE collected for **whole population** to address the uncertainties in HST31 – see Appendix for summary of clinical evidence
- Under HST framework, QALY weighting is driven by undiscounted lifetime QALY gains, inherently sensitive to the age at which treatment is initiated. As adults have fewer remaining years in which benefits can accrue, treatment initiated later in life generates lower undiscounted lifetime QALY gains, even where clinical benefit is meaningful → including the whole population is appropriate to avoid inequity concerns

Abbreviations: BBS, Bardet-Biedl syndrome; ICER, incremental cost-effectiveness ratio; MC4R, melanocortin-4-receptor; QALY, quality-adjusted life years; RWE, real world evidence

Key issue: Population for decision problem (2/2)

Large ICER impact (population)

EAG: whole population not directly relevant to decision problem but noted equity issue

EAG comments – appraisal should focus on adults who did not start treatment as children and not a mixed age population

- Co-base case is not directly relevant to decision problem specified in the NICE scope
- Because a QALY weight applies to paediatrics (1.73) but not adults (1), co-base case ICER is substantially lower than (almost half) that of base case in adults only
- Suggested Other issue on potential age-related inequity; defined 2 adult populations (existing adults without access – catch up, and future people diagnosed as adults)
- **Model starting age for adults** (small ICER impact)**:** Company assumed 20 years. But some BBS diagnosed as adults, so starting age likely to be higher. EAG explores:

28 years (preferred based case)	35 years (scenario)
Newly diagnosed adults: based on mean age in trial and approximation of adults in HSinBBS study obese subset	Catch-up adults: mean age of adults in UK BBS registry

Should adults be assessed separately from the whole population? Which population is preferred for the base case? How should company co-base case be used? What is the appropriate model starting age for adults?

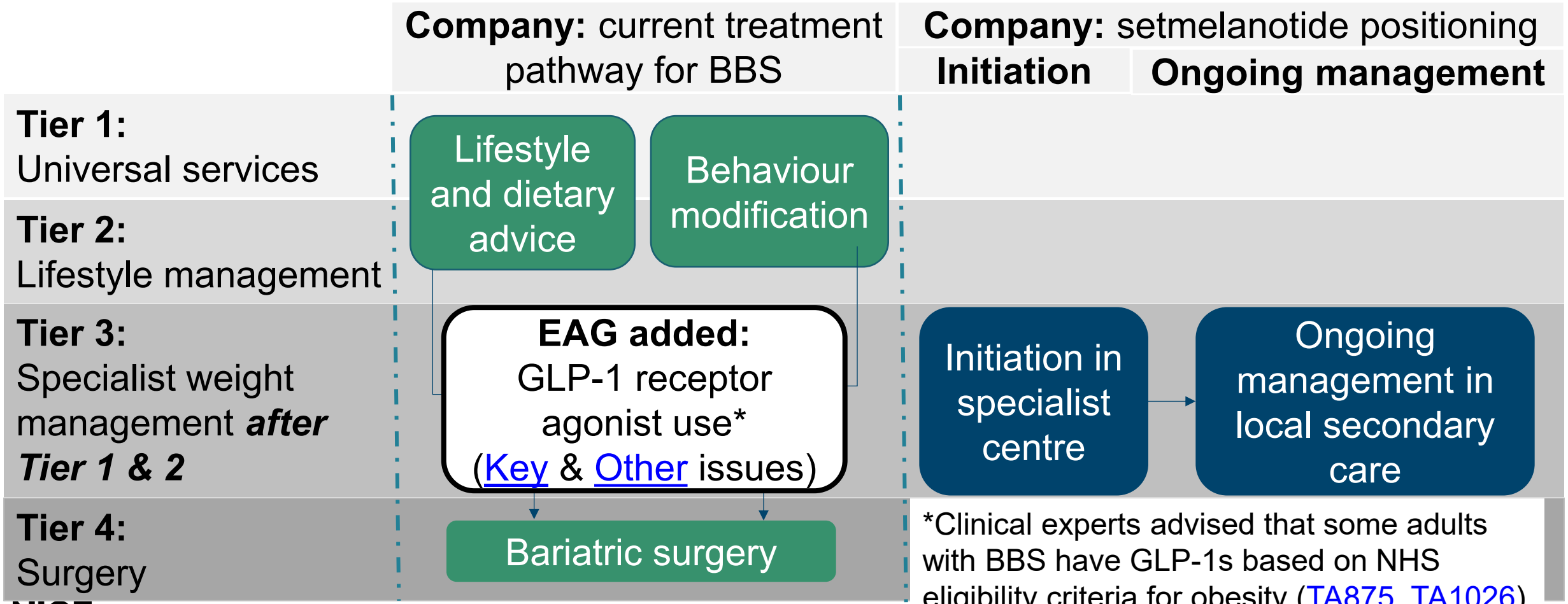
Abbreviations: BBS, Bardet-Biedl syndrome; HSinBBS, hyperphagia severity in BBS study; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Management of BBS in the NHS

See Appendix: Technology (setmelanotide)

EAG: for adults, setmelanotide would be offered at Tier 3 of general obesity pathway (with lifestyle, dietary, exercise advice), initiated through specialist service

- No guideline or clinical pathway specific to BBS, general obesity guideline is used



Abbreviations: BBS, Bardet-Biedl syndrome; GLP-1, glucagon-like peptide-1

Unknown ICER impact

Key issue: Relevance of GLP-1 receptor agonists for adults living with BBS obesity and hyperphagia (1/2)

Company: no suitable evidence available on GLP-1s in BBS, use is opportunistic

Comparator in NICE scope: 'Established clinical management without setmelanotide (including a reduced-calorie diet and increased physical activity)'. **Tech team note:** Does not exclude GLP-1 receptor agonists if they are part of established clinical management

Clinical expert comments

- GLP-1s not currently universally available in NHS, substantial geographic variation

Company – considered EAG questions about GLP-1s at clarification stage

- No RCTs, observational studies or RWE comparative data on use of GLP-1s in BBS
- Efficacy and safety of GLP-1 receptor agonists for treatment of obesity have not been established in patients living with BBS, either because genetic forms of obesity were excluded from trials, or there were not reported patients living with BBS in those trials
- GLP-1s do not address underlying disease mechanism, MC4R pathway of hyperphagia
- Opportunistic use: ~30–50 adults with BBS receive GLP-1s from a single specialist centre, but ~20% receive them for diabetes, which setmelanotide would not replace

Abbreviations: BBS, Bardet-Biedl syndrome; GLP-1, glucagon-like peptide-1; ICER, incremental cost-effectiveness ratio; MC4R, melanocortin-4-receptor; RWE, real world evidence

Key issue: Relevance of GLP-1 receptor agonists for adults living with BBS obesity and hyperphagia (2/2)

EAG: GLP-1s may mitigate inequity, but not currently available to all BBS patients

EAG comments – being successfully in clinical practice for adults with BBS

- Queen Elizabeth Hospital Birmingham specialist centre has several years of data on ~50 people – sample size is similar to that of setmelanotide trials
- Clinical advice from Birmingham centre was that GLP-1s were prescribed within commissioning rules for obesity and related comorbidities, and used where eligibility criteria for BMI and weight-related comorbidities were met
- Clinical advisers thought age-related inequity in access to setmelanotide could be mitigated by availability of GLP-1 receptor agonists for adults (see Other issue)
  - But GLP-1s not currently available to all BBS patients, either via specialist BBS centres or Tier 3 weight management services
- Potential cost saving with GLP-1s (weekly injection) vs setmelanotide (daily injection)

How are GLP-1s being used for obesity and hyperphagia in BBS? Are they part of established clinical management for obesity and hyperphagia in BBS?
If available, would setmelanotide be started in adults having a GLP-1 receptor agonist for obesity management? Would they be used in combination?

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; GLP-1, glucagon-like peptide-1; ICER, incremental cost-effectiveness ratio

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  - New evidence
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- ❑ Other considerations
- ❑ Summary

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See Appendix for HST31 recap: trials and results

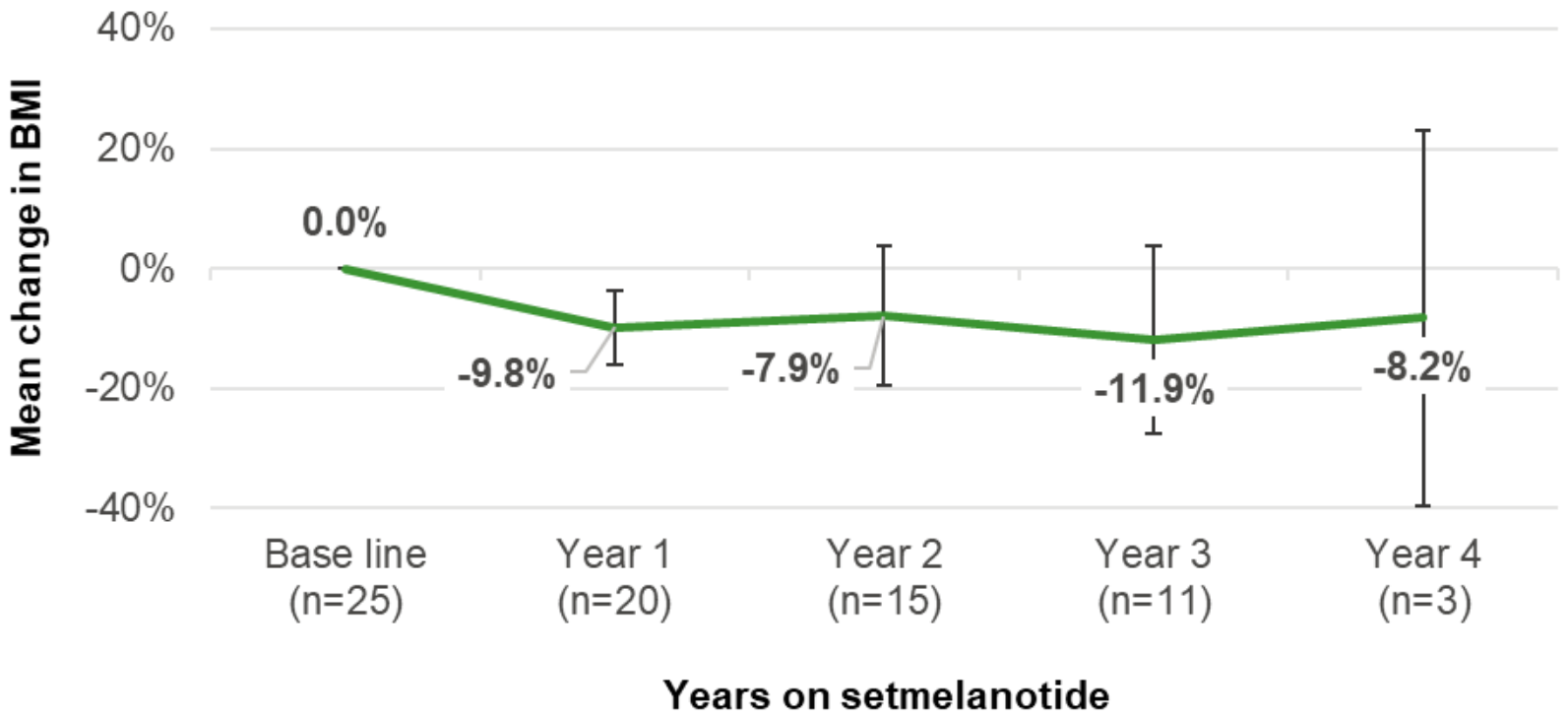
Clinical trial results: new evidence on weight related outcomes (1/2)

Longer-term data available for adults and combined population since HST31

Table. Results of RM-493-022 trial – a Phase 3 LTE study (Poster: Argente et al 2026)

Setmelanotide outcome	4 years (adults, n=3)	5 years (combined, n=4)
Mean % change from baseline in **BMI**	**-8.2% (SD=31.3%)**	-8.8% (SD=22.0%)

Figure. Mean change in BMI in adult patients living with BBS, hyperphagia and obesity in 4 years following setmelanotide initiation (Poster: Argente et al 2026)



Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; LTE, long-term extension; SD, standard deviation

Clinical trial results: new evidence on weight related outcomes (2/2)

EAG: uncertainty in evidence at 4- and 5-year trial follow up and in other sources

EAG comments – company's studies most appropriate sources to inform model

- As in HST31, results from RM 493-022 trial do not directly inform company's model. But year 4 and 5 follow up data are used to support company's assumptions for longer term weight trajectories of patients treated with setmelanotide – a key uncertainty in HST31
- Notes very small numbers of participants at 4- and 5-years follow up, and that outcome is mean change in % BMI and not % change in bodyweight (as reported in HST31)
- 5-year follow-up data are only reported for combined population, not for adults
- Single arm, observational before-after study design for other 2 studies reporting on weight outcomes in adults:
  - Mifsud et al. 2025 (n=11): body weight decreased by 14% at 6 months and 20% at 12 months in people starting setmelanotide at study entry. Hühne et al. 2026 (n=11): weight loss of 8.2 kg (95% CI 6.46; 9.97) at 6 months

What is committee's view on whether the company's evidence adequately addresses uncertainties associated with setmelanotide's treatment effect in adults:

- Its treatment effect on weight-related outcomes?
- Its long-term treatment effect?

Abbreviations: BMI, body mass index; CI, confidence interval

Evidence from other sources: treatment effect on hyperphagia, hunger and other outcomes

EAG: substantial uncertainty in setmelanotide's treatment effect on hyperphagia, hunger, and liver and kidney disease remained

Outcome	Company's new evidence	EAG comments
Hyperphagia	4 additional studies that **do not directly inform model** Findings are broadly consistent, and indicate an improvement in hunger / hyperphagia following setmelanotide treatment for BBS • See Background for summary of studies	Broadly agrees. But studies do not provide confirmatory evidence that setmelanotide reduces hyperphagia in people with BBS, obesity & hyperphagia • Only 2 single arm studies assess hyperphagia directly • Other 2 studies report hunger or eating behaviour as proxies
Liver and kidney disease	Data **directly informs model** • Prospective, observational cohort study in people with BBS (Hühne et al. 2026)	Source lacks comparative data – only included people taking setmelanotide • See Key issues 6 and 7 for how evidence included in model

Abbreviations: BBS, Bardet-Biedl syndrome

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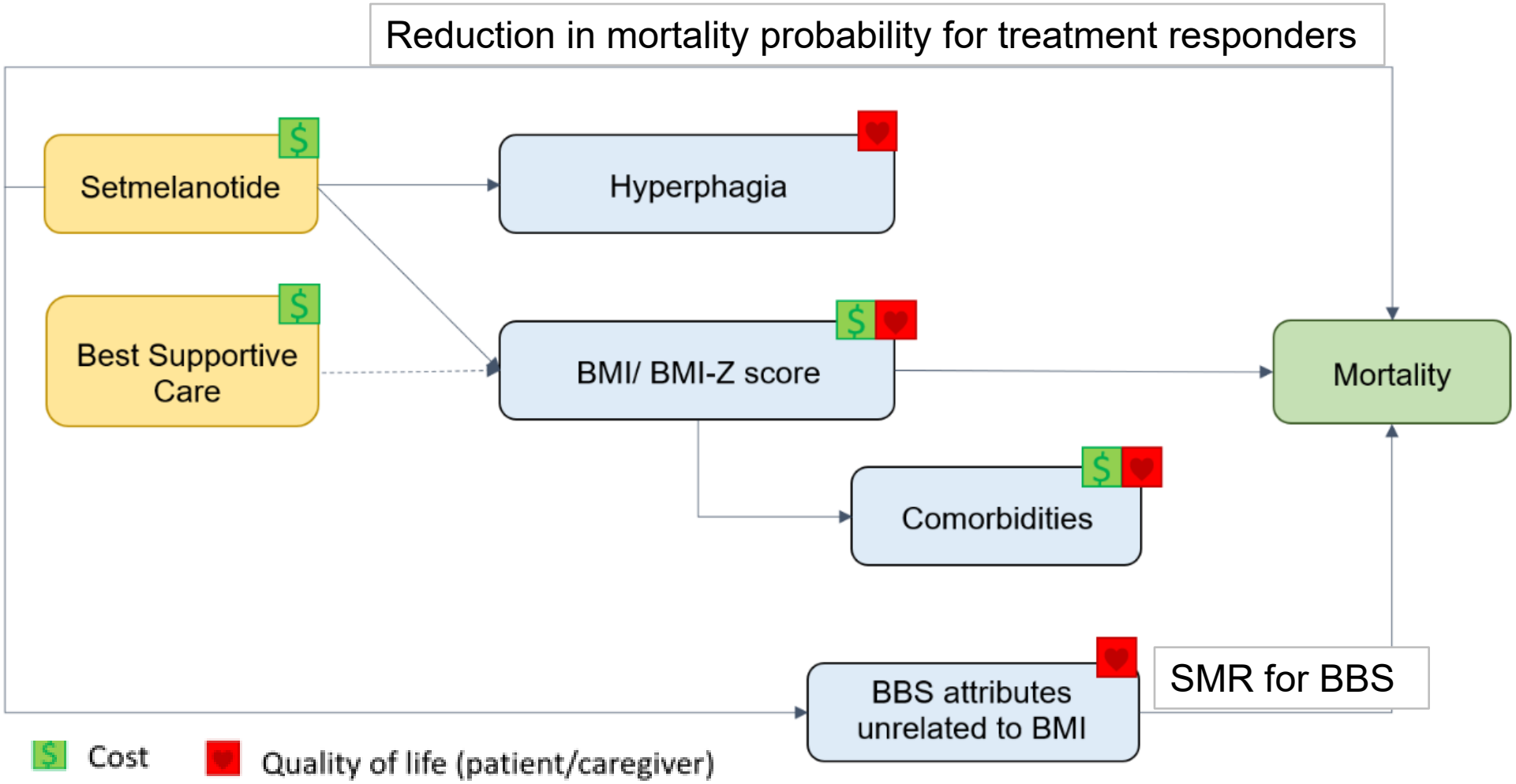
Company's model overview

See Appendix for model features

Figure. How costs and QALYs accrue in the company's model – same as HST31



EAG comments

- Model structure is appropriate
- Modelling of treatment effect reasonable and in line with committee preference [in HST31] and the longer-term evidence

Note: BMI score used for adults / BMI Z score used for paediatrics

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; QALY, quality-adjusted life years; SMR, standardised mortality ratio

Key issue: Distribution of hyperphagia at baseline for adults (1/2)

Company uses data from a small number of interviews to inform baseline severity

Background on HST31:

- No validated, standardised tool to measure hyperphagia / severity in people with BBS
- Company estimated 75% of patients living with BBS had severe hyperphagia and 25% had moderate, based on clinical option. Committee accepted but noted high uncertainty

Company – updated vs HST31

- Presents results from UK HSinBBS study
- Used data from Mossman et al 2026, which is a sub-sample of participants from HSinBBS study to estimate baseline distribution of hyperphagia severity
- Of 39 people with BBS and BMI ≥30kg/m^2 who were assessed using questionnaires, 13 then had semi-structured interviews

Table. Hyperphagia severity at baseline

Severity level	Interviews (N=13)	Questionnaire (N=39)
Severe	69%	8%
Moderate	31%	51%
Mild	0	41%
	Base case	

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; HSinBBS, hyperphagia severity in Bardet-Biedl syndrome; ICER, incremental cost-effectiveness ratio

Key issue: Distribution of hyperphagia at baseline for adults (2/2)

EAG: maintains company approach but notes uncertainty and large ICER impact

EAG comments – very different estimates depending on method used

- Sub analysis (BMI ≥30kg/m^2) – broadly was representative of UK BBS population
- Agrees that interviews offer an opportunity to probe, clarify, and contextualise responses, so may also have greater construct validity for informing classification of hyperphagia in this population
  - But intended to contextualise, not replace, self-reported questionnaire findings
  - Also, convenience sampling and small interview subsample run risks of selection bias vs broader population
- Retains company's assumption using baseline hyperphagia severity from semi-structured interviews in its base case. But believes truth is somewhere between two distributions, and ICER therefore maybe underestimated in the EAG base-case
- High uncertainty; exploratory analysis shows ICER is very sensitive to this assumption

What is the committee's view of the expected baseline distribution of hyperphagia severity before starting treatment with setmelanotide?
Does using estimates from the interviews seem reasonable?

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; ICER, incremental cost-effectiveness ratio

Transitions between hyperphagia states in model

Company approach partially updated, EAG notes remaining uncertainty

Table. Hyperphagia transitions applied in the modelling

Source/Approach	Transition from Severe hyperphagia	Transition from Moderate hyperphagia
HST31	17% move to Moderate 83% move to Mild	100% move to Mild
Company – partially updated approach, has small ICER impact • Based on 1 expert opinion	Same as HST31	70% move to Mild 30% move to none
EAG base case – alternative approach • Based on clinical advice and limited clinical evidence (Mifsud et al. 2025 and Hühne et al. 2026) • Notes remaining uncertainty	Same as HST31	80% move to Mild 20% move to none (explored 90%/10%)

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What is the committee's preferred approach for hyperphagia transitions?

Moderate ICER impact

Key issue: Estimation of BMI and BMIz class shifts in RM-493-023 trial (1/2)

Company models greater BMI reduction for setmelanotide responders than EAG

7 BMI/BMI Z score categories in model:

- Higher score = ↑ obesity
- Change is a 'class shift'
- HST31 assumed adult responders to setmelanotide had a **BMI class-shift reduction of 1** (most common change seen in adults in RM-493-023 trial at 52 weeks)

0.0 ≤ 1.0
1.0 ≤ 2.0
2.0 ≤ 2.5
2.5 ≤ 3.0
3.0 ≤ 3.5
3.5 ≤ 4.0
≥4

Company – updated approach vs HST31

Updated approach for adults:

- Uses mean BMI change at 52 weeks in trial (single-arm data), then adjusted by mean change in BMI observed with BSC in external control group from CRIBBS registry
- Adult responders have **BMI class-shift reduction of 1.37** (response rate = [redacted])
- Any trial placebo effect is not long-term, while those on BSC revert to original BMI

EAG comments

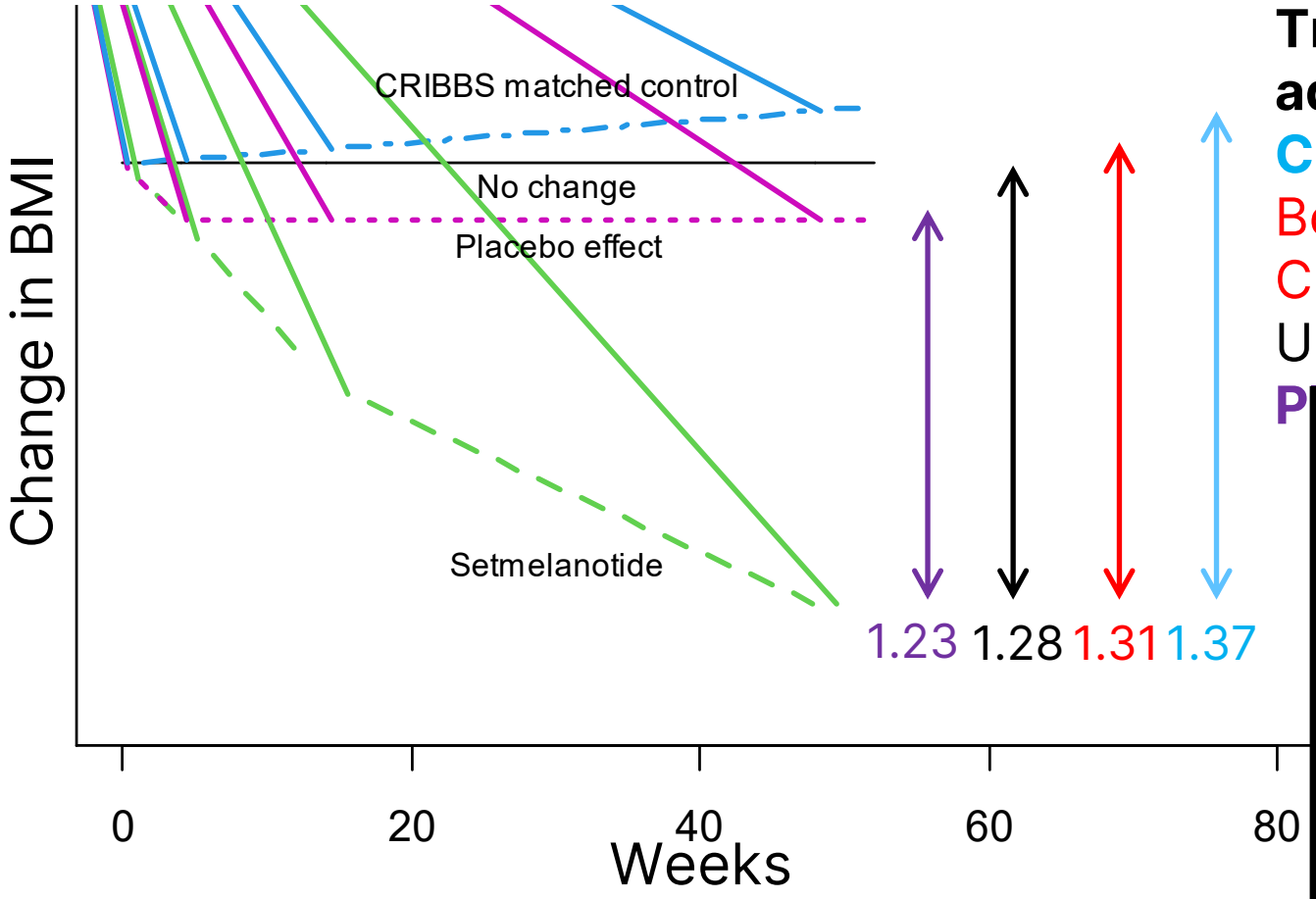
- Has concerns with indirect comparison: limitations with matching, differences in BSC across individuals and settings, and generalisability to a UK context
- Using external control arm does not adjust for artefacts from inclusion in a clinical trial, such as regression-to-the mean, as seen in setmelanotide data (early drop in BMI / BMIz by week 4 before stabilisation in placebo arm up to 14 weeks in RM-493-023)

Abbreviations: BBS, Bardet-Biedl syndrome; BSC: best supportive care; BMI, body mass index; CRIBBS, Clinical Registry Investigating BBS; ICER,

Key issue: Estimation of BMI and BMIz class shifts in RM-493-023 trial (2/2)

EAG: prefers to adjust for trial placebo effect at 14-week, 1.23 BMI class-shift reduction

Figure. EAG's representation of how the treatment effect of setmelanotide on BMI is modelled. Illustrative only and not based on exact figures



Treatment effect adjustment:

- **Company base case**
- **CRIBBS adjusted** ← EAG scenario
- Both placebo and CRIBBS adjusted ← EAG scenario
- Unadjusted ← **EAG base case**
- **P**

EAG comments continued

- Prefers to adjust for trial placebo effect at 14 weeks – based on a randomised comparison, corrects for regression-to-the-mean effect
- Company's approach also different in paediatric population, no BSC/placebo adjustment is made (Key assumptions)

What is the committee's preferred approach?

Abbreviations: BMI, body mass index

Moderate ICER impact

Key issue: Potential additional effect of setmelanotide on MASH beyond effect on MASH due to change in BMI

Company models treatment effect on MASH beyond that on BMI, EAG removes it

Company – updated approach vs HST31

- Hühne et al. 2026, prospective cohort study of setmelanotide for BBS: showed MASLD resolved for 54% of patients, and stabilised at grade S1 hepatic steatosis for 27%
- Modelled a reduction in MASH due to setmelanotide, beyond that due to BMI reduction → assumed 81% reduction factor in MASH for all resolved and S1 patients
  - Incorporated costs and disutilities for MASH into model

EAG comments

- Hühne et al. 2026, statistical analyses not adjusted for change in BMI, so it is unclear if there is an additional effect of setmelanotide beyond that through BMI
- Clinical advisors: not plausible there would be a benefit to MASLD beyond that caused by weight loss. Even if there was, EAG would not expect it to be >54% reduction (patients whose MASLD resolved). Suggests reanalysis of Hühne data could be done
- Explored using 54% reduction factor, but prefers excluding setmelanotide's additional effect on MASH beyond BMI (company's scenario)

Is it reasonable to model an addition effect of setmelanotide on MASH beyond than seen through BMI reduction. If so, how should this be modelled?

Moderate ICER impact

Key issue: Potential additional effect of setmelanotide on kidney disease beyond effect on kidney disease due to change in BMI

Company models treatment effect on kidney disease beyond BMI, EAG removes it

Company – updated approach vs HST31

- Hühne et al. 2026: showed that patients kidney function improved on setmelanotide
- Company incorporated costs and disutilities for kidney function category into model

EAG comments

- Multiple methods to calculate eGFR, including depending on whether measured in under 25s or older adults; produce different results – see Appendix: Estimating eGFR
- Company's preferred approach was analysis that only included patients <25 years of age, using CKiD, which it then applied to whole population. Largest treatment effect
- EAG considers method that measures eGFR in adults and under 25s more suitable
- Change in BMI not incorporated in eGFR analysis, so whether effect of setmelanotide on kidney function was additional to effect mediated by change in BMI is unclear
- Clinical advice: no independent effect of setmelanotide on eGFR expected beyond BMI
- EAG removed effect on kidney function to avoid double-counting, explored in scenarios

Is it reasonable to model an addition effect of setmelanotide on kidney function beyond than seen through BMI reduction? If so, how should this be modelled?

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Abbreviations: BMI, body mass index; CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio

Key issue: Setmelanotide treatment discontinuation rate (mainly relevant for the whole population)

Company assumes treatment discontinuation rate of 1%, EAG prefers 3.42%

Company

- Retains discontinuation rate of 1% for responders to setmelanotide based on HST31
- Considers approach is supported by new evidence, including 2 real world cohorts

EAG comments

- Follow-up data from company's OLE study gives discontinuation rates of 0.6% due to AEs, and 4.5% when voluntary withdrawals are included → provides plausible range
- Company considers voluntary withdrawals may be due to study or personal factors, not efficacy or tolerability, so were excluded. EAG unclear of relevance to clinical practice
- EAG meta-analysis of trial and RW cohorts gave 3.42% rate → preferred for base case
- Acknowledges RWE included non-responders and 1 cohort was BBS and related genetic conditions. But 3.42% is within plausible range; range is explored in scenarios
- EAG's assumption of higher discontinuation rate led to small reduction in ICER for adult population, but large increase in ICER for the whole population (↓ QALY weight)

What treatment discontinuation rate for setmelanotide should be used in model?

NICE

Abbreviations: BBS, Bardet-Biedl syndrome; ICER, incremental cost-effectiveness ratio; OLE, open-label extension; RWE real world evidence

Key issue: Disutility due to non-obesity related BBS symptoms

Company approach based on prevalence of visual and cognitive impairments, EAG notes large ICER impact and suggests testing for validity

Company – updated approach vs HST31

- Modelled disutility due to other non-obesity related symptoms of BBS is based on the prevalence of visual and cognitive impairments seen in RM-493-023 trial
  - Attributed disutilities to these from a UK catalogue of EQ-5D-3L utility population
- Presents scenario for the approach taken in HST31 – this was to apply a QALY multiplier of 0.87, which was derived from mapped PedsQL data in RM-493-023

EAG comments

- Company's updated approach seems reasonable → including disutilities due to visual and cognitive impairments in trial avoids mapping PedsQL data from very small samples
- But EAG notes ICER is very different (lower) than that obtained using HST31 approach
- Suggests that prevalence estimates for visual and cognitive impairments from other cohorts, for example BBS UK, could be used to validate those observed in trial

Is the committee satisfied with the company's approach to modelling disutility due to non-obesity related BBS symptoms?

NICE

Abbreviations: BBS, Bardet-Biedl syndrome; EQ-5D-3L, EuroQol 5-dimension 3-level; ICER, incremental cost-effectiveness ratio; PedsQL, Pediatric Quality of Life Inventory; QALY, quality-adjusted life year

Other issue: Evidence source for impact of BMI on utilities in children (relevant for the whole population only)

Company uses updated data for utilities in children, EAG prefers HST31 approach

Company – updated approach vs HST31

- Used EQ-5D-3L data measured on UK adult patients (mean age 53) undergoing a weight-loss intervention, to obtain utilities by BMI / BMIz category (Breeze et al. 2022)
- Consider that this overcomes limitations with approach taken in HST31 where PedsQL scores in children from Riazi 2010 were mapped to EQ-5D by BMIz for paediatrics

EAG comments

- Agrees with company that Breeze study is preferable source for adults, but considers that impact of BMIz on HRQoL may be different in children than adults of mean age 53
- EAG therefore prefers to use scores for children from Riazi 2010, in line with HST31
- Provides scenarios for combined population using (i) Riazi 2010 mapped PedsQL scores or (ii) Breeze 2022 for paediatric utilities

What approach to deriving impact of BMI on HRQoL in children should be used in model (for the combined population)?

Abbreviations: BMI, body mass index; EQ-5D(-3L), EuroQol 5-dimension (3-level); ICER, incremental cost-effectiveness ratio; PedsQL, Pediatric Quality of Life Inventory

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

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

Other issue: Application of QALY weight in probabilistic results

Company applies averaged weighted QALYs within PSA, EAG disagrees

Company – applies QALY weight at each iteration of probabilistic analyses

- Multiple QALY weights averaged to obtain mean weighted incremental QALYs → **average QALY weight of 1.05** for adult population (vs 1 for adults in HST31)

EAG comments – prefers simpler application of QALY weight outside of PSA

- Company's approach captures uncertainty in the QALY weight but means there is not a single QALY weight that has been applied. NICE manual unclear on preferred approach
- Company referenced HST35: but in this committee wished to capture high uncertainty around QALY weight (range 1–3), which was likely not affected by being truncated at 1
- EAG considers this to be a non-standard application of QALY weight, which is typically computed based on the average undiscounted QALY gain, giving a single QALY weight, which is then applied to average incremental QALYs → EAG **single QALY weight of 1**
- Because QALY weight cannot go below 1, the QALY weight the company use is pushed upwards in adult population. This 'rewards' uncertainty and reduces probabilistic ICER

How should QALY weighting be applied in the probabilistic results?

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; 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

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

See Appendix for Other key assumptions

Key differences in company and EAG preferred assumptions

Table. Assumptions in company and EAG base case

Assumption	Company	EAG	ICER impact
Adult mean age starting treatment	20 years	28 years	Small
BMIz class-shift reduction for adult responders Key issue: BMI class shift	1.37 (external BSC adjustment)	1.23 (with placebo adjustment)	Moderate
BMIz class-shift reduction for paediatric responders	1.74 (no placebo adjustment)	1.56 (with placebo adjustment, =HST31)	Moderate
% responders with moderate hyperphagia moving to mild/none	70% to mild 30% to none	80% to mild 20% to none	Moderate
Treatment discontinuation rate	1%	3.42%	Small (adults) Large (whole)
Additional treatment effect on MASH beyond BMI effect	Included (costs and disutility)	Excluded	Moderate
Additional treatment effect on kidney function beyond BMI effect	Included (costs and disutility)	Excluded	Moderate
Application of QALY weighting	Within PSA (~1.05)	Outside PSA (1)	Moderate

Abbreviations: BMI, body mass index; MASH, metabolic dysfunction-associated steatohepatitis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years

Summary of cost-effectiveness results

Adult initiator population – base case:

- Company and EAG ICER is substantially above £100,000 / QALY
  - QALY weight =1 (incremental undiscounted QALYs <10)
- Overall result not changed in scenarios
  - Largest impact is Baseline distribution of hyperphagia severity (and Population)

Whole population – company's co-base case:

- Company: Weighted ICER is below £100,000 / QALY (incr. undiscounted QALYs ~17); unweighted ICER substantially above £100,000 / QALY
- EAG: ICER substantially above £100,000 / QALY (incr. undiscounted QALYs ~9)
- Overall results not changed in scenarios except treatment discontinuation rate, where company's weighted ICER moves above £100,000 / QALY if discontinuation rate of 2.28% or higher is assumed

All ICERs are reported in Part 2 slides because they include confidential discounts

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

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (review of HST31) [ID6598]

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
  - Equality
  - Uncaptured benefits
- ❑ Summary

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Equality considerations (1/2)

Table. Summary of stakeholder submissions (including at scoping and in HST31)

Theme	Issue raised	Committee at ACM1
Age See also Other issue on *inequity*	Hyperphagia persists into adulthood with cumulative metabolic and psychosocial burden. Equitable access to setmelanotide across the lifespan should be considered	HST31 negative recommendation for adults was proportionate to NICE's legitimate aims
Disability	BBS is associated with visual impairment, learning disability and physical complications, which may affect ability to self-inject daily and manage treatment Poor mental health & stigma affects access to support	Need for accessible delivery system, appropriate training and additional support is noted, but could not be addressed by a NICE recommendation
Race and Ethnicity	Setmelanotide affects skin pigmentation – may influence treatment decisions, particularly where skin tone changes carries cultural or social significance	Noted, but treatment effects on skin tone could not be addressed by a NICE recommendation

- Note: The same issue themes were considered in HST31

Abbreviations: BBS, Bardet-Biedl syndrome

Equality considerations (2/2)

Table. Summary of stakeholder submissions (including at scoping and in HST31)

Theme	Issue raised	Committee at ACM1
Genetic status (from clinical experts in HST31)	Setmelanotide license is for 'genetically confirmed BBS'. But some people (20%) do not have identifiable pathogenic gene variants and are identified clinically	Noted, but committee could not make a recommendation outside of the licensed population for setmelanotide
Socio-economic context	Those with limited resources or reduced access to structured support may experience greater difficulty managing persistent hyperphagia and obesity	Access to NHS healthcare, specialist services and national commissioning are not implementation issues that could be addressed by a NICE recommendation
Geographic variation	Access to therapies used to manage obesity or diabetes varies between regions	

- Note: The same issue themes were considered in HST31

Does the committee's think there are any other equality issues to be considered that have not been considered here (including in Key issue 2)?

Abbreviations: BBS, Bardet-Biedl syndrome

Other issue: Potential inequity concern given HST31 recommendation

EAG: variation in timing of diagnosis and the progressive nature of BBS

EAG comments

- Clinical experts at HST31 committee meeting: “a substantial proportion of people are diagnosed and start treatment for BBS as adults in current clinical practice”
- Diagnosis ages vary, reflecting heterogeneous and progressive nature of BBS.
  - Subset patients diagnosed as adults: data from recent CRIBBS cohort showed median age at diagnosis of 5.8 years, but with very wide range (0 to 43 years)
- 2 groups of adults impacted when considering age of starting setmelanotide:
  - Current ‘catch-up’ adults diagnosed in childhood and still meet eligibility criteria but did not have access to setmelanotide at that time (retrospective exclusion)
  - Future newly diagnosed as adults, or those diagnosed as a child but hyperphagia and obesity criteria not met until they are adults (prospective exclusion)
- Clinical advice: inequity may be mitigated by availability of GLP-1 receptor agonists for adults, but limited by phased roll out and local variation

What is the committee’s view of the inequity concerns? Do timing of diagnosis and the progressive nature of BBS raise equality issues around age? Is there a potential equality issue around age specifically in adults, that is different from considerations made in HST31? (see Equality considerations)

Abbreviations: BBS, Bardet-Biedl syndrome; CRIBBS, Clinical Registry Investigating BBS; GLP-1, glucagon-like peptide-1

Potential uncaptured benefits (1/2)

Several potential uncaptured aspects proposed, but EAG notes uncertainty

Clinical expert submission:

- Impact on hyperphagia beyond BMI likely to improve patient function, quality of life and satisfaction → may not be captured fully by QALY calculation

Company comments	EAG response
Model does not capture all obesity-related comorbidities. Presents some evidence on impact of setmelanotide on reduced metabolic syndrome severity score	Impact of setmelanotide broader than specific co-morbidities that are modelled, although these will already be captured to some extent through utilities and costs associated with higher BMI state
Approach to modelling improved or delayed progression of kidney and liver disease is conservative. Costs of dialysis not included	Unclear if additional effect beyond changes in BMI, and whether already captured for costs and utilities through associated with BMI class

Abbreviations: BMI, body mass index; QALY, quality adjusted life year

Potential uncaptured benefits (2/2)

Several potential uncaptured aspects proposed, but EAG notes uncertainty

Company comments continued	**EAG response**
Setmelanotide may be associated with improvements in cognitive and affective function, limited evidence from Germany	Any benefit on cognitive function currently uncertain, but is not captured in model. Clinical advisors noted potential benefit through weight loss (seen with GLP-1s), but direct biological effect implausible
Immunomodulatory benefit beyond weight loss not captured	Setmelanotide unlikely to have additional effect immunomodulatory
Wider family QoL benefits of reducing hyperphagia	Benefits for wider family (siblings) not included. Carer-giver HRQoL is included
Financial burden associated with BBS, indirect costs of obesity on lost work for patients and carers, and higher food bills	"Productivity costs should be excluded from the reference case." Committee may consider as additional information

Does the committee's think there are any uncaptured benefits to be considered?

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Abbreviations: BBS, Bardet-Biedl syndrome; GLP-1, glucagon-like peptide-1; HRQoL< health-related quality of life; QoL, quality of life

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (review of HST31) [ID6598]

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues for discussion

	Key issue	ICER impact
Decision problem	Population for decision problem	Large (population) Small (adult age)
	Relevance of GLP-1 receptor agonists for adults living with BBS obesity and hyperphagia	Unknown
Model	Distribution of hyperphagia at baseline for adults	Large
	Estimation of BMI and BMIz class shifts	Moderate
	Potential additional effect of setmelanotide on MASH beyond effect on MASH due to change in BMI	Moderate
	Potential additional effect of setmelanotide on kidney disease beyond effect on kidney disease due to change in BMI	Moderate
	Setmelanotide treatment discontinuation rate	Small (adults) Large (whole population)
	Disutility due to non-obesity related BBS symptoms	Large

Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome (review of HST31) [ID6598]

Supplementary appendix

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Back to Treatment pathway

Setmelanotide (IMCIVREE, Rhythm Pharmaceuticals)

Marketing authorisation	• Granted: "For the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) […] in adults and children 2 years of age and above." • Also has a marketing authorisation in loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency
Mechanism of action	• A selective MC4 receptor agonist that activates the MC4R neuron, to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure
Administration	SC injection into abdomen at a different site; once daily at start of day • Adults and paediatric ≥16 years: up to 3mg/day • Paediatric: 6 to <16 years: up to 3mg/day (2 to <6 years not in model)
Price	• List price per pack £2,376 per 10 mg/mL vial • Lifelong treatment. Company considers average annual cost per patient and average dose per day as confidential • Patient access scheme is applicable

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

BBS is characterised by early onset severe obesity and hyperphagia

- **Symptoms:** vary by frequency and onset
- **Diagnosis:** Relies on presence of clinical symptoms (4 primary or 3 primary features and 2 secondary features)
- **Confirmation:** Following clinical diagnosis, BBS is confirmed in approximately 80% of patients using genetic testing
    - Testing for rare genetic obesity available in NHS

Table: Diagnostic features of BBS and frequency

Primary features	
Rod-cone dystrophy	93%
Extra digits	63% to 81%
Obesity	**72% to 92%**
Genital anomalies	59% to 98%
Renal anomalies	53%
Learning difficulties	61%
Secondary features	
Speech delay	54% to 81%
Developmental delay	50% to 91%
Diabetes mellitus	6% to 48%
Dental anomalies	51%
Congenital heart disease	7%
Shortening of digits	46% to 100%
Joining of digits	8% to 95%
Ataxia/poor coordination	40% to 86%
Anosmia	60%

Abbreviations: BBS, Bardet-Biedl syndrome

Back to Key issue 1 on Population age group

Appendix: Clinical evidence builds on that presented in HST31

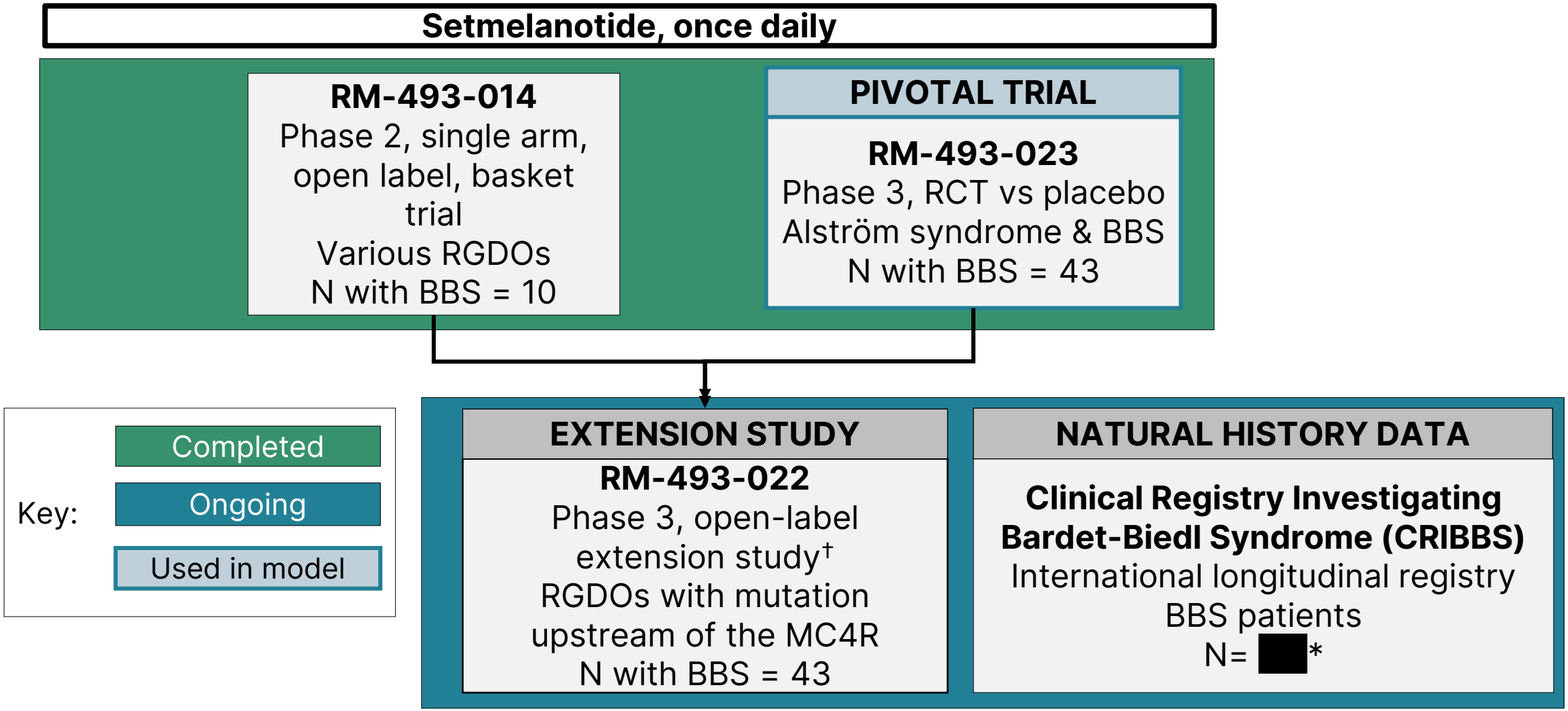
Includes longer term trial data, some reanalysis and other supporting evidence

Company's clinical evidence submission	Used in model?
To address uncertainty noted in HST31:	
• Effect of setmelanotide on weight related outcomes, specifically: Potentially overestimated due placebo effect/ regression to the mean Very limited data on maintenance of treatment effect over longer term	Yes: company trial results with longer-term data
• Hyperphagia (5 relevant studies identified): Proportion of adult patients living with BBS, hyperphagia and obesity who experience severe hyperphagia Effect of setmelanotide on hyperphagia symptoms and patient QoL	Yes: for baseline severity data But treatment effect not applied
• Carers quality of life (background evidence only)	No: not applied
• Effect of setmelanotide on metabolic syndrome (reanalysis of trial)	No: not applied
Other evidence:	
• Effect of setmelanotide on liver disease and kidney disease in BBS	Yes: Hühne study

Abbreviations: BBS, Bardet-Biedl syndrome; QoL, quality of life

RECAP: Overview of clinical trials

Back to Clinical trial results (new)



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

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

Key results for weight related outcomes

Back to Clinical trial results (new)

Single arm results suggest body weight and BMI reduction with setmelanotide

Table. Results of RM-493-023 trial – a Phase 3 RCT with OLE (as applied in HST31)

Setmelanotide outcome at 52 weeks (single arm OLE period)	**Patients aged ≥18 years**	**Patients aged <18 years**
Proportion of patients who achieved ≥10% bodyweight reduction from baseline	[redacted] (n=15)	N/A
Change in BMI after 52 weeks of treatment		
Mean change in BMI from active-treatment baseline	4.22 kg/m^2	3.36 kg/m^2
Mean percent change in BMI	9.09%	9.50%

Clinical expert comment: proportion of study participants achieving 10% weight loss from baseline is a valid outcome which is clinically relevant

Abbreviations: BMI, body mass index; OLE, open label extension; RCT, randomised controlled trial

Back to Clinical trial results (new)

Results include new evidence on weight related outcomes

Longer-term data available for adults from RM-493-022 trial since HST31

Table. Results of RM-493-022 trial – a Phase 3 LTE study
(*As applied in HST31. New results: †Yanovski et al 2023; ‡Argente et al 2026)

Setmelanotide outcome	1 year (adults)	2 years (adults)	3 years (adults)	4 years (adults)	5 years (combined)
Mean % change from baseline in body weight	[redacted] (SD=[redacted]) (n=[redacted])*	[redacted] (SD=[redacted]) (n=[redacted])*	−15.3 (SD=11.5) (n=10)†	N/A	N/A
Mean % change from baseline in BMI	[redacted]% (SD=[redacted]%) (n=[redacted])‡	[redacted]% (SD=[redacted]%) (n=[redacted])‡	[redacted]% (SD=[redacted]%) (n=[redacted])‡	-8.2% (SD=31.3%) (n=3)‡	-8.8% (SD=22.0%) (n=4)‡

RECAP of HST31

Abbreviations: BMI, body mass index; LTE, long term extension; SD, standard deviation

Back to Company's model overview

Appendix: Company's model features

Lifetime model:

- Disease states are 7 BMI / BMI Z-score categories, and death
- Setmelanotide treatment alters distribution of patients across BMI / BMI Z-score categories
- Higher BMI / BMI Z-score increases mortality risk
- On discontinuation of setmelanotide, patients revert to original BMI / BMI Z-score category in BSC arm
- 1 year cycle, half-cycle correction
- 3.5% discount rate is used for both costs and health effects

Assumptions with greatest ICER effect:

- Whether model restricts to adult initiators of setmelanotide
- Baseline distribution of hyperphagia severity before initiating setmelanotide
- Approach taken to model impact of non-obesity BBS symptoms on utilities
- Inclusion of kidney disease comorbidity

Abbreviations: BMI, body mass index; BSC, best supportive care; ICER, incremental cost-effectiveness ratio

Back to Key differences in assumptions

Other key assumptions in company and EAG modelling

Table. Assumptions in company and EAG base case continued

Assumption	Company	EAG	ICER impact
Population in base case	**Adult population** (Company: co-base case for Whole population)		Large (vs whole)
Baseline hyperphagia severity in base case & source	**By interview: 69% severe, 31% moderate, 0 mild** (EAG explored By questionnaire: 8% severe, 51% moderate, 41% mild)		Large (vs questionnaire)
Disutility due to non-obesity related BBS symptoms in base case	**RM-493-023 trial prevalence of visual and cognitive impairments, with disutilities applied (EQ-5D-3L), UK** (Company scenario for HST31 approach: QALY multiplier of 0.87, derived from mapped PedsQL data in RM-493-023)		Large (vs HST31)
Evidence source for impact of BMI on utilities in children	**Breeze 2022**: paediatric utilities by BMI category, which uses EQ-5D-3L data in UK adults	**Riazi 2010**: PedsQL utilities, then mapped to EQ-5D for paediatric utilities (=HST31)	Small (only relevant to whole population)

Abbreviations: BMI, body mass index; MASH, metabolic dysfunction-associated steatohepatitis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years

Back to Key issue: Kidney disease

Alternative approaches for estimating eGFR for effect on kidney

Multiple methods to calculate eGFR, and company preferred approach has largest treatment effect where effect in under 25s applied to whole population

Table. Estimates of baseline eGFR and change in eGFR at 6 months reported in Hühne et al. 2026 by method of calculation

eGFR calculation method	Population	Mean eGFR before initiating setmelanotide	Change in mean eGFR at 6 months on setmelanotide (95% CI)
Creatinine; CKD-EPI[a]; bedside Schwartz[b]	All	101.1	9.64 (4.51, 14.77)
Creatinine + cystatin C; CKD-EPI[a]; CKiD[b]	**All**	84.1	**7.61** (4.12, 11.08)
Creatinine; EKFC[a]	Adults	88.9	6.95 (3.59, 10.30)
Creatinine + cystatin C; EKFC[a]	Adults	79.0	4.23 (-0.47, 8.87)
Creatinine; CKiD[b]	**Under 25s**	90.9	**10.12** (4.31, 15.93)
Creatinine + cystatin C; CKiD[b]	Under 25s	83.1	6.60 (2.14, 11.06)

*EAG preferred method; but EAG excluded from model

EAG*

Company

Key: [a]Adults; [b]Under 25s

Abbreviations: CKiD, Chronic Kidney Disease in Children; EKFC, European Kidney Function Consortium; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval

Back to Company base case results

Model corrections by EAG

EAG made corrections to company's model at clarification stage and after company submission

EAG comments – very different estimates depending on method used

- EAG identified an error in calculation of MASH cost which was doubly inflated (clarification question B15)
  - This was corrected in company's model following clarification → company updated base case
- EAG then performed a model validation of company's updated model – identified 3 issues in the model file during validation checks, plus a further issue in how QALY weighting applied – see Other issue
  - Correction of 3 issues is applied in the results for → EAG corrections to company base case
  - EAG also provided results for alternative interpretations of QALY weighting application

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; QALY, quality-adjusted life year