PART 1 for public contains no confidential information

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

Chairs presentation

Chair: Peter Jackson

Evidence Review Group: Bristol TAG

Technical team: Emma Douch, Ewa Rupniewska, Jasdeep Hayre

Company: Rhythm Pharmaceuticals

December 2023

NICE

Timeline: ID3947, setmelanotide for BBS

RECAP

Aug 2023: negative DGC published

Oct 2023: negative FDG prepared but not published

ECM1, July 2023

- High uncertainty in modelling
- Committee preferred ICER not presented

Additional info requested:

- Alternative ways to capture variability in treatment effect on hyperphagia & BMI
- Exploring potential regression to mean

ECM2, Sep 2023

Setmelanotide not cost effective against BSC even with QALY weighting

Post ECM2:

- New PAS after commercial negotiations
- New clinical expert info on hyperphagia response to treatment: committee preferred assumption updated

ECM3, Dec 2023

- **Update to PAS**
- **New baseline hyperphagia statuses**
- **Further claims for conservative nature of model (incl. no. carers)**

BSC, best supportive care, BMI, body mass index; DGC, draft guidance consultation; ECM, evaluation committee meeting; FDG, final draft guidance; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life-year

Link to supplementary appendix: background and the technology

Committee conclusions ECM2, cost effectiveness

Topic	Company ECM2	EAG's ECM2	Committee conclusion/consideration ECM2
Baseline hyperphagia	75% severe, 25% moderate	60% severe, 40% moderate	No evidence that those with moderate hyperphagia wouldn't have setmelanotide: prefer EAG's approach
Treatment effect on hyperphagia for responders	Moderate or severe at baseline: 100% to mild	Moderate at baseline: 100% to mild Severe at baseline: [redacted]% to mild, [redacted]% to moderate	**Committee updated preferred assumption post ECM2 based on new clinical opinion:** EAG scenario: [redacted]% severe move to mild, [redacted]% move to moderate hyperphagia (using more granular classes for BMI-Z of >4)
BMI-Z drop for responders	[redacted] -level BMI-Z class	[redacted]-level BMI-Z class	EAGs approach preferred as accounts for placebo effect.
Number of carers	[redacted]	[redacted]	1 carer for adult people with BBS should be modelled

BMI, body mass index; ECM, evaluation committee meeting

Link to supplementary appendix: committee conclusions ECM2, clinical effectiveness and model structure

ECM2: conclusions and recommendations

Other considerations by committee	
QALY weighting	QALY weighting criteria likely to be met
Preferred ICER	£224,272 per QALY gained.
Committee conclusion	Not cost-effective when considering QALY weighting

Recommendation

1.1 Setmelanotide is not recommended, within its marketing authorisation, for treating obesity and hyperphagia in genetically confirmed Bardet-Biedl syndrome (BBS) in people aged 6 years and over.

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BMI, body mass index; ICER, incremental cost effectiveness ratio; QALY, quality of life years; QoL, quality of life

Company’s new information

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Company's response & key issues for discussion

Company agrees with committee preferred assumptions except baseline hyperphagia severity, provides updated patient access scheme & further justification for conservative nature of model

Committee conclusion ACM2	Company's updated base case	Company scenarios	Impact
Baseline hyperphagia severity: 60% severe, 40% moderate	86% severe, 14% moderate	75% severe and 25% moderate[a]	5-10K
1 carer for adults with BBS	As per committee's preferred assumption	[redacted] carers for adults with BBS	<5K

Key issues for discussion

1. Are the company's updated baseline hyperphagia statuses preferred for decision making?
2. Are there any new benefits highlighted by the company that aren't captured in the model?

   2a. Is the committee's preferred number of carers for adults with BBS an underestimate?

[a] base case at ECM2; ECM, evaluation committee meeting

Company's response: baseline hyperphagia status (1)

Background (FDG section 3.17):

- Hyperphagia not captured in trials & no standard scale to grade severity
- Can't consistently identify severe hyperphagia: may use setmelanotide in moderate disease
- No evidence on % with moderate hyperphagia + obesity who would have setmelanotide
- ***Prefer:*** EAG's base case baseline hyperphagia severity of 60% severe, 40% moderate hyperphagia (distribution of severities in clinical practice according to company experts)

Company: acknowledge uncertainty due to lack of clear definition of eligible population

- Consulted with BBS UK: 60:40 is hyperphagia severities in overall NHS population (regardless of obesity)

Out of 100 people with BBS[a]	60 have severe hyperphagia	40 have moderate hyperphagia
70 live with obesity	60[b]	10
30 no obesity (not in MA)	0[b]	30

Table: company's updated hyperphagia calculations

Of people living with obesity:

- 60/70 (**86%**) have severe hyperphagia
- 10/70 (**14%**) have moderate hyperphagia

[a] Sources: BBS UK survey 2020/21; BBS UK survey 2022; [b] Assumes all people with severe hyperphagia have obesity.

Company's response: baseline hyperphagia status (2)

Company (cont.): assuming 86% severe and 14% moderate hyperphagia conservative:

- Responders beyond 14 weeks likely have severe hyperphagia (expect to see greater benefit from setmelanotide as likely have more severe obesity)
- Clinical experts: vast majority of people treated will have severe hyperphagia
  - These people present more frequently, are more likely to be referred to specialist services & are prioritised for treatment as known to clinicians

EAG: Company's estimates assume surveys on the same population, and responders are representative of full BBS population.

- Also assumes that none of the BBS population in either survey have mild hyperphagia.
- Implies 75% of people with moderate hyperphagia would have mild or no obesity, which is implausible -> suggests survey also included people with mild hyperphagia
- EAG considers the proportion of severe to be lower.

Prefers: company scenario with 75% severe, 25% moderate at baseline

- Is the committee minded to reconsider baseline hyperphagia severity distribution based on the company's response?

Link to supplementary appendix: baseline hyperphagia status slide, ECM2

Company's response: Conservative nature of the model (1)

Background (FDG section 3.27): committee acknowledged model may be conservative and several benefits of setmelanotide may be underestimated

Company: submitted further argumentation for model being conservative

Company base case	Company's response ECM3	EAG response
Immediate return to baseline state when stop treatment	Model doesn't account for weight gain in untreated patients	Also doesn't account for weight gain in people who **are** treated: size of uncaptured benefit unclear
[redacted]% severe move to mild, [redacted]% move to moderate hyperphagia	**New** clinical expert opinion: expect no hyperphagia in a % with BMI-Z drop >2 / responders with moderate baseline hyperphagia	Variability across hunger scores in trial. Some people will move to no hyperphagia, and some will move to moderate hyperphagia. Effect unclear.

BMI, body mass index; ECM, evaluation committee meeting

Link to supplementary appendix: previously discussed conservative aspects of the modelling and factors affecting the guidance

Company's DG response: Conservative nature of the model (2)

Company (cont):

Company base case	Company comment ECM3
1 carer for adult BBS patients (aligned with committee preference at ACM2)	Nº carers for adults with BBS likely underestimated in base case: • Clinical expert opinion, ECM1: 1-2 carers per adult patient • EAG research: 0-2 carers per adult patient **New: *Scenario using***: • [redacted] carers for moderate hyperphagia (from BBS UK survey) • [redacted] carers for severe hyperphagia (company assumption) Weighted average using new baseline hyperphagia = [redacted] carers

EAG: recognise uncertainty in nº carers for adult patients & that this will vary in practice

- Content that company's new base case aligns with committee preferred assumptions

- Are there any **new** benefits highlighted that are not captured in the company's model and should be factored into decision making?
- How plausible is the company's updated number of carers for adults with BBS?

Cost-effectiveness results

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Updated assumptions in company base case

Assumption	Company base case	Company scenario	EAG base case	Impact
Baseline hyperphagia severity status	**New:** 86% severe, 14% moderate	75% severe and 25% moderate (base case ECM2)	75% severe and 25% moderate	5-10K
Number of carers for adult patients	1 (committee preferred)	**New:** [redacted]	1 (committee preferred)	<5K

Link to supplementary appendix: full list of assumptions in the company base case

ECM, evaluation committee meeting; QALY, quality adjusted life year

Company & EAG CE analyses (mixed population, replicated by EAG)

Probabilistic analyses in the mixed population (60% paediatrics, 40% adults)

	Inc. costs*	Inc. QALYs*	Inc. undiscounted QALYs	ICER	Weighted ICER
Committee preferred base case post ECM2 with new PAS	[redacted]	[redacted]	[redacted]	**£171,091**	[redacted]
Company updated base-case†	[redacted]	[redacted]	[redacted]	**£155,436**	[redacted]
Company scenarios					
[redacted] carers adult patients	[redacted]	[redacted]	[redacted]	**£149,897**	[redacted]
75% severe & 25% moderate hyperphagia at baseline **(EAG base case)**	[redacted]	[redacted]	[redacted]	**£161,596**	[redacted]

*costs and benefits discounted at 3.5%. EAG could not replicate exact ICERs reported by company – EAG's replicated ICERs reported here. †Uses committee preferred assumption where [redacted]% of severe move to mild & [redacted]% to moderate hyperphagia. BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Link to supplementary appendix: CE analyses in paediatric population, full list of assumptions in the company base case and criteria for applying QALY weighting

Decision making framework

1	What are the committee's preferred assumptions on ❖ Baseline hyperphagia distribution ❖ Number of carers for adults
2	Are there any new uncaptured benefits that should be considered?
3	What is the committee's preferred ICER threshold?
4	Should QALY weighting apply?
5	Therefore, using bullets 2+3, what is the committee's preferred ICER?

5	Is the ICER below the preferred ICER threshold? If yes, can this be recommended for routine commissioning (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold)?
6	If not, could the key uncertainties be sufficiently resolved during a period of managed access? If so: • Has the company made a managed access proposal? Is this considered feasible? • Has the committee answered the questions in NICE's feasibility assessment? • What is committee's preferred threshold for managed access? • Which ICERs/assumptions represent committee's lower/upper end of uncertainty?
7	• What, if any, are the key remaining uncertainties?

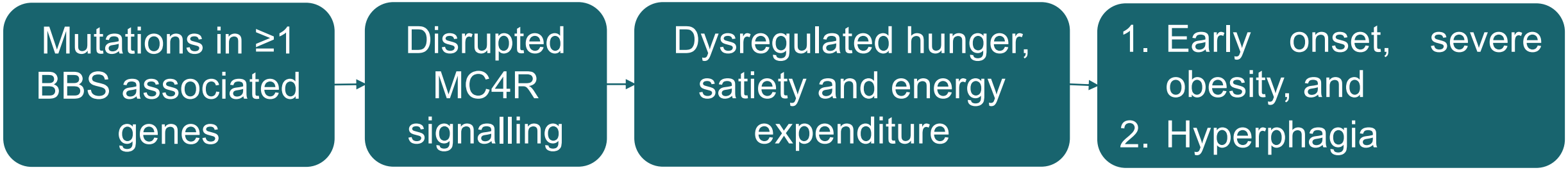
Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome

Supplementary appendix

Disease background: Bardet-Biedl syndrome (BBS)

RECAP

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



Symptoms: Wide range of symptoms: vary by frequency and onset

- Obesity and related comorbidities (type 2 diabetes, heart disease), learning difficulties, visual impairment, kidney problems, extra toes or fingers, and genital or hormonal problems

Quality of life: Associated with large QoL impact and multiple comorbidities. Key QoL impact from: obesity and hyperphagia; depression, social isolation and social stigma; vision loss

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

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

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

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

Link to main slides: study timeline

Setmelanotide, Imcivree®

Link to main slides: study timeline

RECAP

Marketing authorisation	Licenced for "the treatment of obesity and the control of hunger **associated with genetically confirmed Bardet-Biedl syndrome (BBS)** […] in adults and children 6 years of age and above." Setmelanotide also has a marketing authorisation in loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency
Mechanism	Activates MC4R neuron, which decreases appetite & increases satiety
Administration	Subcutaneous injection into abdomen at a different site; once daily
Dosage	Summary of product characteristics details daily dosing based on age:

Age, years	Week 1	Week 2*	Week 3 and onwards*
6 to < 16	1 mg	2 mg	3 mg
>16	2 mg		3 mg

*Dose escalation subject to previous dose being well tolerated.

Duration	Long-term use
List price	List price £2376 per 10mg vial. Update to confidential simple patient access scheme proposed

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

FDG: committee conclusions, clinical effectiveness

RECAP

Topic	Committee conclusion
Nature of condition	• Severe condition associated with multiple comorbidities • Hyperphagia all-consuming and debilitating • Associated with poor mental health for patients, carers and families • Substantial burden on carers to implement strict diet and exercise regime
Population	Company's population narrower than MA (severe hyperphagia only). • % with severe hyperphagia and how identified in clinical practice uncertain: whole population in the MA likely offered treatment.
Comparator	BSC only: bariatric surgery & semaglutide unlikely to be used in BBS patients
Outcomes	Key clinical trials likely generalisable but hyperphagia not measured
Stopping treatment	• Company's definition of response based on changes in weight/BMI • Clinical experts: response determined by changes in behaviour associated with severe hyperphagia in clinical practice at 14 weeks
Clinical effectiveness	• Short-term: may improve obesity-related outcomes, hunger scores & QoL • Long-term: uncertain, very few people with 36 month follow up in OLE • No hunger & HRQoL data vs. placebo at 14 weeks. No carer HRQoL.

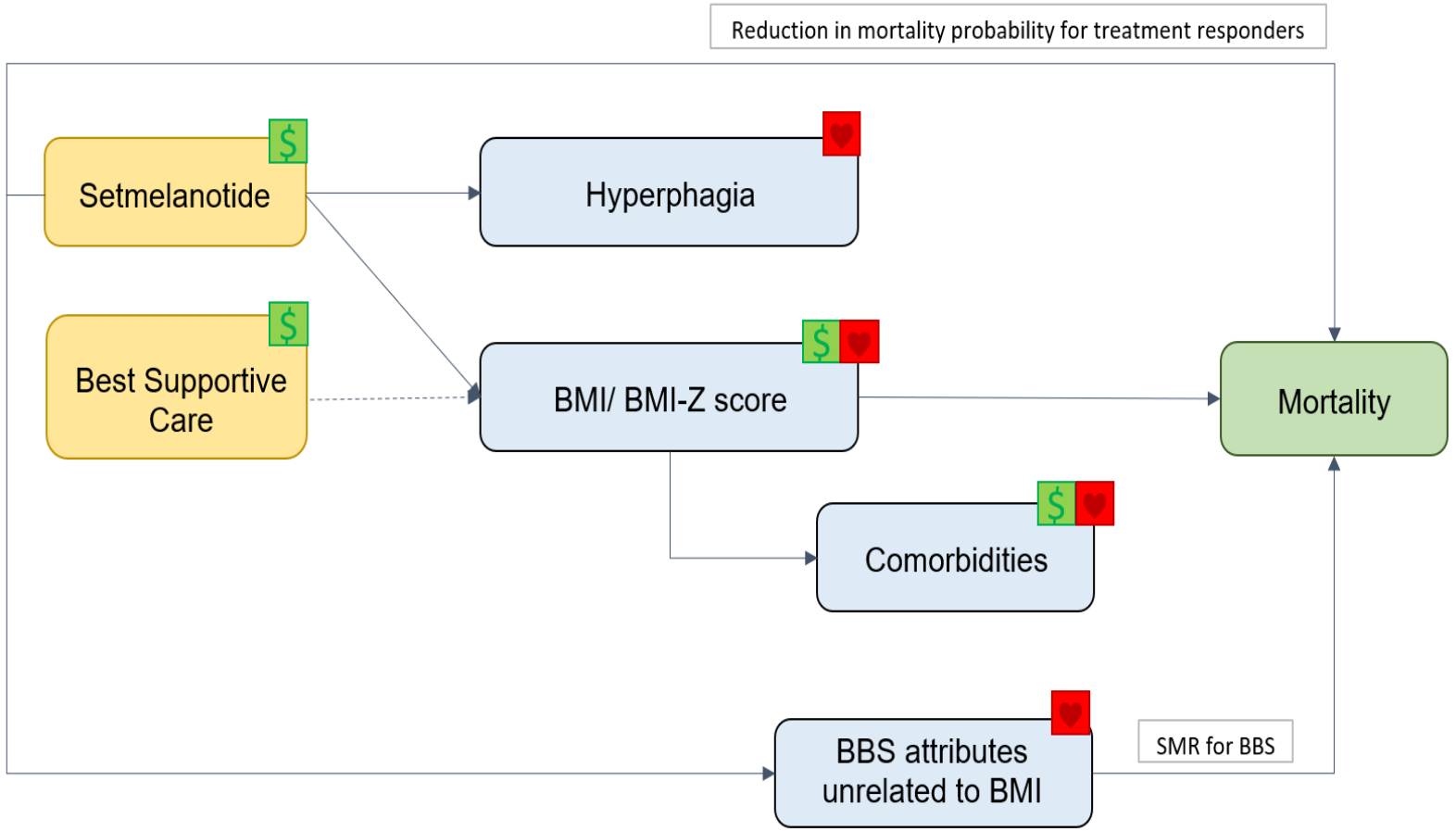
HRQoL, health related quality of life; MA, marketing authorisation; OLE,

Link to main slides: committee conclusions, cost effectiveness

Model structure

Link to main slides: committee conclusions ECM2

How costs and QALYs accrue in the company's model



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

Cost

Quality of life (patient/caregiver)

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

Recap from ECM2: Baseline hyperphagia distribution

Background (DGC section 3.15): Company's population = severe hyperphagia only:

- MA & clinical trials include all severities
- No scale for assessing hyperphagia severity -> identification relies on clinical judgement

Committee conclusion: moderate hyperphagia likely treated in clinical practice & included in trials. Full MA population should be considered.

Populations considered for setmelanotide

Population	Preferred by	Baseline in model
Severe hyperphagia only	Company	100% severe hyperphagia
Mix of severe & moderate hyperphagia	EAG (but could not model in ECM1 base case), committee	60% severe, 40% moderate (expert opinion of split in clinical practice)

Company: Maintain that moderate & severe patients identifiable in clinical practice:

1. BBS diagnosed in specialist centres by MDTs (clinicians, psychologists, nutritionists) -> experience in differentiating hyperphagia severities
2. Clear differences between moderate & severe hyperphagia identifiable by experienced clinicians:
   - E.g. eating large number of calories at night: severe = almost every night, moderate = ~2-3 x per week
   - Don't need specific assessment tool: diagnose severity by weight, maladaptive & food seeking behaviour

Acknowledge committee preference for mix of baseline severities but % with severe hyperphagia higher:

- Higher disease burden so prioritised for treatment.
- **Base case**: 75% severe and 25% moderate hyperphagia

EAG: no new info presented on identification of hyperphagia severities: maintain view that all patients in MA likely considered for treatment, regardless of severity.

- **Base case**: 60% severe, 40% moderate hyperphagia

DCG, draft guidance consultation; MA, marketing authorisation; MDT, multidisciplinary team

Link to main slides: Baseline hyperphagia status

Conservative nature of the model (3)

Link to main slides: New company justification

ACM2: Committee acknowledged model is conservative. Previously considered below:

Company model	Company's response	EAG response
Some comorbidities not modelled	Some uncaptured comorbidities of early onset obesity affect QoL (dyslipidaemia, anxiety, depression, asthma, cancer dermatological complications, reproductive disorders & infections	Company's model may underestimate HRQoL benefits from treating comorbidities
Obesity related comorbidity rate	EOObesity-model (ECM2) predicted: • Untreated patients: ↑ comorbidity & mortality rates vs. base case. • ↑ life year & QALY gains vs. base case with setmelanotide	Support using BBS patient's data but concerns re EOObesity generalisability. Unclear what model inputs from children
Upper limit of BMI classes >4	Doesn't capture comorbidity & mortality benefits for very high BMI / BMI-Z scores	Likely underestimates the benefits for these patients
Immediate return to baseline when stop treatment	Non-responders = no benefit in year 1 & those stopping after 52 weeks immediately lose benefit: tapering of benefit likely	Lack of waning may outweigh benefit lost by company's modelling of discontinuation

BMI, body mass index; ECM, evaluation committee meeting; EOObesity, early onset obesity; QALY, quality adjusted life years; QoL, quality of life

Factors affecting the guidance

Link to main slides: New company justification

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

Nature of the condition

- Extent of disease morbidity & patient clinical disability with current care
- Impact of disease on carers' QoL
- Extent and nature of current treatment options

Clinical effectiveness

- 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

- 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

Impact beyond direct health benefits

- 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 & 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

Full list of assumptions in the company and EAG base cases

Assumption	Company base case	EAG base case
Baseline hyperphagia severity status	86% severe, 14% moderate	75% severe, 25% moderate
Assumptions updated at consultation accepted by both company and EAG		
Population	Mixed (60% paediatrics, 40% adults)	
Treatment effect on BMI-Z in children	[redacted]-level BMI-Z class drop	
Treatment effect on hyperphagia	Moderate at baseline: 100% to mild Severe at baseline: [redacted]% to moderate, [redacted]% to mild	
Health state utilities	Derived from Riazi et al.	
BBS multiplier	[redacted] (mapped from RM-493-023 PedsQL scores)	
Number of carers for adult patients	1	

BMI, body mass index; PedsQL, Pediatric Quality of Life Inventory; QALY, quality adjusted life year

Link to main slides: Company & EAG analyses in mixed population

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

Link to main slides: Company & EAG analyses in mixed population

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

Company and EAG CE analyses (paediatric population)

Probabilistic analyses in the paediatric population (all people enter the modal aged 6)

	Inc. costs*	Inc. QALYs*	Inc. undiscounted QALYs	ICER
Committee preferred base case post ECM2 (with new PAS)†	[redacted]	[redacted]	[redacted]	**£166,676**
Company updated base-case†	[redacted]	[redacted]	[redacted]	**£151,235**
Company scenarios				
[redacted] carers adult patients	[redacted]	[redacted]	[redacted]	**£146,763**
75% severe & 25% moderate hyperphagia at baseline **(EAG base case)**	[redacted]	[redacted]	[redacted]	**£157,330**

*costs and benefits discounted at 3.5%. EAG could not replicate exact ICERs reported by company – EAG's replicated ICERs reported here. †Uses committee preferred assumption where [redacted]% of severe move to mild & [redacted]% to moderate hyperphagia
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Link to main slides: cost effectiveness results in mixed population