National Institute for Health and Care Excellence

Highly Specialised Technology (HST)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Rhythm Pharmaceuticals	Yes, it is appropriate to refer this product for NICE appraisal. However, we believe evaluation via the STA route is not appropriate for setmelanotide and setmelanotide should be evaluated via the HST programme. Setmelanotide is indicated for the treatment of hyperphagia and obesity in Bardet-Biedl syndrome (BBS) or Alström syndrome (AS), two ultra-rare genetic conditions. The treatment fulfils all seven of the current criteria for consideration via the HST programme: **1.For both indications (BBS and AS) setmelanotide will be used exclusively within the context of a Highly Specialised Service (the**	Comments noted. The HST criteria was considered by the topic selection panel who deemed the criteria met. The company have since withdrawn Astr**ö**m syndrome from the proposed indication in its application to the EMA.

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		service for Bardet Biedl Syndrome and the service for Alström Syndrome) and through a very limited number of centres: • Birmingham Women's and Children's Hospital NHS Foundation Trust (BBS and AS) • Great Ormond Street Hospital for Children NHS Foundation Trust (BBS) • Guy's and St Thomas' NHS Foundation Trust (BBS in adults) • University Hospitals Birmingham NHS Foundation Trust (BBS and AS in adults) **2.The target population is very small - approx. 250 patients eligible with BBS and approx. 40 paediatric patients eligible with AS (see below)** The population for treatment for both indications is determined by the licence which requires confirmation by genetic testing. The numbers of patients eligible for treatment are broken down as follows (with advice sought and received from the treating centres and the relevant patient groups): <u>In BBS</u> • Whilst exact prevalence data is unknown it is estimated and published that BBS has a prevalence of ~1 in 100,000 *(BBS UK)* Most patients are already diagnosed • It is estimated there is a TOTAL population of 472 in England (560 in UK) *(data from BBS UK)* • Of these, 72 – 92% are likely to have obesity *(Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013;21:8–13. PubMed PMID: 22713813.)*	

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		• Use of setmelanotide will require genetic confirmation. Approximately 20% of individuals do not have identifiable pathogenic variants of the known 19 BBS-related genes and therefore would not be appropriate for treatment *(**NLM Citation:** Forsythe E, Beales PL. Bardet-Biedl Syndrome. 2003 Jul 14 [Updated 2015 Apr 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019)* • Therefore, this will give a range of 272 – 340 patients as a maximum. • The licence will apply to patients over the age of 6 years of age (estimated to be 95% of patients by the treating centres) – a population of 258 - 323 • The treating centres have identified an estimated 20 % of patients have chronic renal failure and will be unsuitable for treatment This suggests a patient population for BBS in the range of **206** to a maximum of **258.** <u>In AS</u> In UK there are 85 known patients *(UK)* and Alström when this is extrapolated to England this equates to 70 patients (approximately 40 paediatric patients and 30 adults).	

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		• Prevalence publications in AS refer to fewer than 1:1,000,000 in populations with low levels of consanguineous marriages. *(*Alström *Syndrome Clinical Management Guidelines, 2014)* • In the pivotal phase III clinical trial, the primary end point data for adult Alström patients did not achieve significance. [redacted] We therefore suggest the **maximum number of potential patients for the AS indication is 40.** **Taken together the eligible BBS and AS populations for setmelanotide are estimated to be between 246 and 298 patients.** **3.The target patient group is clinically distinct** **There are a number of distinctive clinical features:** For BBS 3 or 4 of the following primary clinical features are documented in the clinical diagnosis • Rod-cone dystrophy • Polydactyly • Obesity • Learning disabilities • Hypogonadism in males • Renal anomalies	

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		For AS the following clinical features are the most common and are documented in the diagnosis: • Retinal Degeneration (inherited progressive eye disease) • Nystagmus (wobbly eyes) • Photophobia (sensitivity to light) • Sensorineural Hearing Loss (disorders of the cochlear part of the ear) • Obesity and Insulin Resistance In addition to the distinct clinical features the target population is genetically distinct and will be confirmed with a genetic test (genetic testing is included in the setmelanotide draft license indication) A common distinguishing clinical feature of both BBS and AS is hyperphagia - an uncontrollable insatiable hunger which leads to obesity and has a significant impact on a patient's quality of life *1.Chacko SA et al. Prev Med.2015;72:89-94* *2.Kleinendorst L, et al BMJ case rep 2017* *3.Kuhnen P, et al N ENG J Med, 2016; 375:240-246* **4.The condition is chronic and severely disabling** Any of the clinical features of BBS and AS described above may themselves be severely debilitating. A key clinical feature common to both AS and BBS is hyperphagia which leads to obesity in the majority of patients and a range of subsequent conditions impacting morbidity and mortality. There are no licensed	

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		treatments targeting hyperphagia or obesity and without effective treatment and support these conditions will progress. <u>Hyperphagia</u> Hyperphagia is an overwhelming, heightened, and relentless hunger, mimicking feelings of starvation, a longer time to reach satiety and shorter duration of satiety, severe preoccupation with food, persistent and potentially extreme food-seeking behaviours (e.g. night eating, stealing food, and eating non-food items) and distress or inappropriate behavioural response if denied food. Hyperphagia negatively impacts quality of life, with patients reporting being so preoccupied with food and the desire to eat that it dominates their life, affecting concentration, productivity and education. <u>Obesity and high BMI</u> Hyperphagia leads to excess energy intake and lifetime weight gain. The association between high BMI and mortality has been well documented, Compared with individuals of healthy weight (BMI 18·5–24·9 kg/m^2), life expectancy from age 40 years was 4·2 years shorter in obese (BMI ≥30·0 kg/m^2) men and 3·5 years shorter in obese women *(Lancet Diabetes Endocrinol 2018; 6: 944–53 Published Online October 30, 2018)* A high BMI also has a significant impact on morbidity; some examples include : long term morbidities such as CV disease and cancer; children can also develop sleep apnoea and they may have lung development and musculoskeletal problems both of which are disabling. In addition to the physical impact there is significant psychological impact on patients. *(Narang I, Mathew JL Journal of nutrition and metabolism. 2012;2012.)*	

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		5. The acquisition cost is high Setmelanotide has an approved list price of £2,376 for one 1ml vial (each 1ml vial consists of 10mg setmelanotide) and the maximum dose per day is 3mg; we estimate an average of 110 vials per year per patient. There is a Commercial in Confidence (CiC) PAS for the MHRA approved PPL indication (estimated **15** patients in England). Whilst a (CiC) PAS is expected to be put in place for BBS and AS, the anticipated per patient acquisition cost for the small number of patients will be relatively high in comparison to treatments for larger patient populations. **6. The condition is chronic and the treatment will be required for life long use.** BBS and AS result from genetic mutations and have a profoundly negative chronic impact on patients. Setmelanotide acts to restore impaired signalling of the MC4R pathway and helps control the resulting severely disabling symptoms (e.g. hyperphagia and obesity) but does not address the underlying genetic mutations and hence lifelong treatment will be required. **7. National commissioning is essential** National commissioning will be essential to ensure equitable access for a small number of patients and avoid inequity in impact on local NHS resources.	

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	Bardet-Biedl Syndrome UK	Yes	Comment noted.
	NHS England	It is appropriate for this topic to be referred to NICE.	Comment noted.
Wording	Rhythm Pharmaceuticals	We suggest that hyperphagia is written prior to obesity within the text, as obesity is an outcome of the hyperphagia. "Genetically confirmed" should also be added to BBS and AS, as genetic confirmation is critical for patient selection and will be required as part of the licensed indication for setmelanotide.	Comments noted. The remit reflects the trial population and anticipated marketing authorisation wording.
	NHS England	The wording of the remit reflects the issues of clinical and cost effectiveness about this technology.	Comment noted.
Timing Issues	Rhythm Pharmaceuticals	There is no licensed treatment for hyperphagia and obesity for BBS or AS and there is a significant unmet need for patients and their families. Constant and continued hyperphagia has a significant detrimental impact on a patients' quality of life (QoL), as well as the lives of their caregivers, particularly parents looking after their children and trying to control their food intake. Obesity has a cumulative effect over time on the development of co-morbidities and as stated above there is a well-recognised association between high BMI and morbidity and mortality. It is thus important to initiate therapy rapidly.	Comments noted. The appraisal will commence as soon as is possible.
	NHS England	Routine	Comment noted.

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Additional comments on the draft remit	Rhythm Pharmaceuticals	No	Comment noted.

Comment 2: the draft scope

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Background information	Rhythm Pharmaceuticals	Overall, the background information is accurate. However, there are a few points that would benefit from correction: • The background states that 90% of BBS patients show excessive weight gain through the first year of life. This is correct, but not all overweight patients are obese. The label specifically states **obesity** and we believe between 72% - 92% of patients with BBS develop obesity. • The section refers to CG189 and orlistat. The orlistat SmPC states that: "*There is no relevant indication for use of Xenical in children."* In addition there is no data supporting the use of Orlistat in BBS patients or in any patient suffering from Rare Genetic Diseases of Obesity' • Similarly, the section refers to liraglutide. There is no data supporting the use of liraglutide in BBS patients or in any patient suffering from Rare Genetic Diseases of Obesity	Comments noted. The scope now refers to the proportion of people that develop obesity. Liraglutide and orlistat have both been removed as comparators from the scope.
	Bardet-Biedl Syndrome UK	We don't feel visual impairment in BBS is currently given enough emphasis in the description of the syndrome. It is a primary symptom, with the average age of registration of severe sight impairment (blindness) being 15 years of	Comments noted. The scope gives only a brief description of the

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		age. This, coupled with cognitive impairment impacts on the ability to self-administer Setmalenotide, which is via subcutaneous injection.	condition, treatment pathway and epidemiology. Submissions will include more detailed descriptions of the disease and its symptoms
	NHS England	NHS England commissions specific highly specialised services for individuals with Bardet-Biedl syndrome (BBS) and Alstrom syndrome (AS). Services for individuals with BBS are commissioned from four expert centres in England (two for adults and two for children). There were 325 patient assessments undertaken in 2019. The service is listed in chapter 4 of the NHS England Manual for Prescribed Specialised Services. Services for individuals with AS are commissioned from two expert centres in England (one for adults and one for children). The caseload of the service in 2019 was 85. The service is listed in chapter 20 of the NHS England Manual for Prescribed Specialised Services.	Comments noted.
The technology/ intervention	Rhythm Pharmaceuticals	The description of the technology is accurate. Setmelanotide was previously investigated in a phase II study for Prader Willi syndrome but is not currently in development for this condition.	Comments noted. Scope has been amended accordingly.
	NHS England	The description of the technology is accurate.	Comments noted.
Population	Rhythm Pharmaceuticals	As described above, [redacted]	Comments noted. The population in the scope

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		[redacted] The ultra-rare nature of the conditions and low patient numbers preclude the use of subgroup data. There are no subgroups which should be considered separately.	will be in line with the marketing authorisation.
	Rhythm Pharmaceuticals	The evidence submission will address: Patients with genetically confirmed Bardet-Biedl Syndrome, aged 6 years and over, with the following obesity markers: • Adults (aged 18 years and over): body mass index (BMI) 30 kg/m^2 and over • Children and adolescents (aged 6 to 17 years): weight 97th percentile or more for age on growth chart assessment The threshold for obesity also differs slightly from the draft scope which stated: • People aged 16 and over: body mass index (BMI) 30 kg/m^2 and over; • People aged 15 and under: weight 97th percentile or more for age on growth chart assessment	Population updated in response to company's request during the DP meeting. The company clarified that this change was to align with the definitions of children and adults used by NICE and in the NHS. It is also in line with the definition of obesity in HST21.
	NHS England	The population is described accurately.	Comments noted.
Comparators	Rhythm Pharmaceuticals	There is no data supporting the use of Orlistat or liraglutide in BBS patients or in any patient suffering from Rare Genetic Diseases of Obesity (RGDO). Bariatric surgery is not recommended for RGDO patients and does not address the genetic impairment and resulting insatiable hunger; it is also unsuitable for patients with cognitive impairment so these are not appropriate comparators.	Comments noted. Orlistat and liraglutide have been removed as comparators from the scope.

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		Of the remaining comparators no relevant comparator has been left out of the scoping document	It was noted at the scoping workshop that bariatric surgery is occasionally used in some patients with BBS so has been left in as a comparator.
	Novo Nordisk	Novo Nordisk would like liraglutide 3.0mg to be excluded as a comparator of this appraisal. The safety and efficacy of liraglutide 3.0mg for weight management have not been established in patients with obesity secondary to endocrinological or eating disorders, therefore, use in these patients is not recommended (Liraglutide 3.0mg SmPC). Novo Nordisk would like to highlight that patients with secondary causes of obesity (i.e., hypothalamic, genetic or endocrine causes) have been excluded in the relevant liraglutide 3.0mg trial (Kelly, 2020, supplementary appendix).	Comment noted. At the scoping workshop it as agreed that liraglutide is not a comparator.
	NHS England	The comparators listed are the standard treatments used in the NHS with which the technology should be compared.	Comments noted.
Outcomes	Rhythm Pharmaceuticals	Yes. However, BMI-z is especially useful in children and adolescents, while weight loss is only useful in adults Co-morbidities such as cancer, CV events and type 2 diabetes will take years to develop, even for obese children and adolescents, and cannot be evaluated as part of a regulatory trial. There is no key outcome missing	Comments noted.

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	NHS England	As well as incidence of Type 2 diabetes clinical measures of diabetic control should be added	Comment noted. 'Clinical measures of diabetic control' has been added to the outcomes in the scope.
Economic analysis	Rhythm Pharmaceuticals	Use of setmelanotide, and hence the appropriate time horizon, is lifelong	Comment noted.
Equality and Diversity	Rhythm Pharmaceuticals	It is our belief that routing via the STA programme is not appropriate and would be discriminatory to a highly vulnerable population with a range of severe disabilities including (in BBS) cognitive impairment. BSS and AS are ultra-rare conditions. The challenges of determining cost effectiveness in very small patient populations is well known. The HST programme, which was designed to address these challenges would be more appropriate and setmelanotide appears to fulfil all the current entry criteria for being considered via this route. BSS and AS affect multiple organs and result in a wide range of potentially severe disabilities, including cognitive disability, visual impairment, renal impairment and the development of diabetes. The consequences of these rare genetic conditions not only affect patients, but also significantly impact their families and caregivers. There is a significant burden particularly on those looking after children with severe hyperphagia. Appraisal via the STA route would compromise the ability of the small number of patients with these rare conditions to access this new technology.	Comments noted. The HST criteria was considered by the topic selection panel who deemed the criteria met. The company have since withdrawn Aström syndrome from the proposed indication in its application to the EMA.

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	Bardet-Biedl Syndrome UK	The means of delivery may exclude some from accessing this medication, for example those who are living independently with a visual impairment would not be able to safely self-administer a sub-cutaneous injection - We would like to see an alternative method of administration for example an epi-pen or similar.	Comments noted. Where appropriate, the committee will consider any potential equality issues identified throughout the evaluation and whether the recommendations make it more difficult for a particular group to access treatment. No changes made the scope.
	NHS England	Both AS and BBS are autosomal recessive conditions and are likely to be more common in communities where there is consanguinity.	Comments noted. Where appropriate, the committee will consider any potential equality issues identified throughout the evaluation and whether the recommendations make it more difficult for a particular group to access treatment. No changes made the scope.

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Other considerations	Rhythm Pharmaceuticals	The key issue is appropriateness of appraisal via the STA route.	Comment noted. The HST criteria was considered by the topic selection panel who deemed the criteria met.
Innovation	Rhythm Pharmaceuticals	Setmelanotide is a highly innovative new treatment with a unique mode of action – a highly targeted action binding to (as an agonist) melanocortin-4 receptor (MCR4) to restore impaired signalling of the MCR4 pathway. The specific management of Rare Genetic Diseases of Obesity is new and setmelanotide therefore represents a significant development Currently there is no licensed therapy for hyperphagia or obesity associated with BBS and AS and setmelanotide will be the first licensed and specific treatment option. Setmelanotide is the first and only therapy which has demonstrated clinical benefits in hyperphagia and obesity associated with BBS and AS. Setmelanotide is the first and only therapy to have demonstrated: • Reduction in BMI (children) /Weight (adults), reduction in hunger and improvement in quality of life in BBS patients • Reduction in BMI-z scores in AS patients <18 years • A reduction in hunger in patients with BBS and AS	Comment noted. The innovative action of this drug is not something discussed at scoping. It will be discussed at committee. Further details on this can be included in the submissions.
	NHS England	Given that there are no targeted obesity treatments for this patient cohort this would represent a useful additional therapeutic option.	Comment noted.

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Questions for consultation	Rhythm Pharmaceuticals	*Appropriateness of appraisal via the STA route.* Whilst we agree that a NICE appraisal of setmelanotide is appropriate we do not agree that the STA route is appropriate. We refer to the comments above, that BBS and AS are rare syndromes and setmelanotide is eligible for between 246 – 298 patients in England and should be evaluated via the HST route to enable a fair and equitable assessment of the clinical and cost-effectiveness. *Difference between BBS and AS* Both BBS and AS are syndromic diseases with a wide variety of symptoms affecting multiple organ systems of the body. Both BBS and AS are “ciliary diseases” However, the genetic cause of the diseases are different as identified by genetic testing, and the specific symptoms are also different. In both diseases hyperphagia and obesity are prevalent symptoms with strong negative impact on QoL. *Impact of the condition on length of life and QoL* There are very little data on life expectancy in BBS and AS. In BBS, one study shows a median survival at 63 years. Reported cases in the literature fail to identify BBS patients over 60 years old and clinical experts agree that BBS patients have shorter life expectancy than comparable non affected patients. The same can be said of AS Quality of life is negatively affected. In our phase III study, adult BBS patients had a QoL at inclusion of 74.9 measured by IWQoL (disease specific tool 0-	Comments noted. The HST criteria was considered by the topic selection panel who deemed the criteria met. The company have since withdrawn Aström syndrome from the proposed indication in its application to the EMA.

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		100 scale), while pediatric patients had had a QoL at inclusion of 67.2 measured by PedsQL (generic pediatric tool 0-100 scale) *Capture of Hyperphagia in QoL* There is no specific tool to capture hyperphagia in QoL. The Vignette study that was used to develop utilities associated to various hyperphagia levels *(data on file)* will be used in the health economic model, mapped to hunger reduction. QoL is measured in adult patients through the Impact of Weight on Quality of Life (IWQoL), an obesity specific quality of life tool and in pediatric patients through Paediatric Quality of Life Inventory (PedsQL), a generic pediatric QoL tool. Neither of these two tools are specifically designed to capture the variations of hyperphagia and /or hunger on QoL *Subgroups* The economic model will address BBS and AS separately. For BBS it will be developed for both adult and paediatric subgroups, [redacted] *Genetic tests* BBS and AS are genetic diseases. No additional genetic testing will be required for the use of setmelanotide, as genetic testing is already an integral part of the diagnosis of these diseases within NHS England. *Additional health Benefits not included in the QALY calculation* There is a significant burden on caregivers particularly caregivers looking after children with severe hyperphagia. In some cases, children's cravings for	

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		food are so overwhelming that parents have no other choice but lock the fridge and cupboards or hide all food items in their homes. The stigma of having an obese child can cause significant distress and parents may blame themselves for not being able to control what their child eats. *Barriers to Adoption* We do not anticipate any specific barriers to adoption	
	NHS England	What is the number of people with BBS and AS, respectively, in England? How many of them will be eligible for treatment (have obesity defined as body mass index [BMI] 30 kg/m^2 and over for aged 16 and over, or 97th percentile or more for age on growth chart assessment for those 15 years and under)? NHS England commissions specific highly specialised services for individuals with Bardet-Biedl syndrome (BBDS) and Alstrom syndrome (AS). Services for individuals with BBS are commissioned from four expert centres in England (two for adults and two for children). There were 325 patient assessments undertaken in 2019. Services for individuals with AS are commissioned from two expert centres in England (one for adults and one for children). The caseload of the service in 2019 was 85. How are BBS and AS clinically distinguished from one another? Through genetic testing. Within the expert centres commissioned by NHS England for the two syndromes, there are some staff who are common to both services and would distinguish individuals phenotypically and genetically.	Comments noted. For those questions related to the HST criteria, these were considered by the topic selection panel who deemed the criteria met. The company have since withdrawn Aström syndrome from the proposed indication in its application to the EMA.

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		What is the impact of the condition on length of life and/or quality of life? No specific comments. Have all relevant comparators for setmelanotide been included in the scope? Which treatments are considered to be established clinical practice in the NHS for BBS and AS? As listed in the scope. Are the outcomes listed appropriate? See above How would the impact of hyperphagia (excessive hunger) be captured in health-related quality of life measures? Questionnaires, eye tracking Are the genetic tests to confirm a diagnosis of either BBS or AS standard practice in the NHS? Yes: BBS R107.1 and R107.2 and AS R106 in the Genomic Testing Directory. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the	

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		proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which setmelanotide will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Both AS and BBS are autosomal recessive conditions and are likely to be more common in communities where there is consanguinity. Do you consider that the use of setmelanotide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Impact on care givers will need careful consideration	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Genetic Alliance UK