



## CADTH Reimbursement Recommendation

# Setmelanotide (Imcivree)

**Indication:** For weight management in adult and pediatric patients 6 years of age and older with obesity due to Bardet-Biedl syndrome

**Sponsor:** Rhythm Pharmaceuticals, Inc.

**Final recommendation:** Reimburse with conditions



# Summary

## What Is the CADTH Reimbursement Recommendation for Imcivree?

CADTH recommends that Imcivree be reimbursed by public drug plans for weight management in adult and pediatric patients 6 years of age and older with obesity due to Bardet-Biedl syndrome (BBS) if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Imcivree should only be covered for patients who are aged 6 years and older and have a clinically or genetically confirmed diagnosis of BBS and obesity.

### What Are the Conditions for Reimbursement?

Imcivree should only be reimbursed if prescribed by an endocrinologist, pediatric endocrinologist, and/or specialist in weight management or obesity and the cost of Imcivree is reduced. When first prescribed, Imcivree should only be reimbursed for 26 weeks. Reimbursement may be renewed on a yearly basis for patients who experience a clinically meaningful decrease in body weight or body mass index (BMI).

### Why Did CADTH Make This Recommendation?

- In 1 clinical trial, treatment with Imcivree reduced body weight in patients with BBS who were at least 6 years of age and who were obese. The results of this study also suggested that Imcivree may reduce hunger.
- Patients identified reductions in body weight and hunger as important outcomes. Based on the evidence reviewed, Imcivree may meet these needs.
- Based on CADTH's assessment of the health economic evidence, Imcivree does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Imcivree is estimated to cost the public drug plans approximately \$23 million over the next 3 years.

## Additional Information

### What Is BBS?

BBS is a rare, incurable genetic disease that causes many symptoms, including hyperphagia, the inability to feel full, and early onset obesity. The prevalence of BBS is estimated to be 1 in 100,000 to 160,000 in North America and Europe, but the disorder occurs with greater frequency



# Summary

in certain regions, such as in Newfoundland and Labrador (where the prevalence is 1 in 16,000 to 18,000).

## **Unmet Needs in BBS**

There are no other therapies available that are indicated for the treatment of BBS. Unrelenting hunger, hyperphagia, and obesity are identified by patients as 3 of the most distressing and impactful symptoms of the disease.

## **How Much Does Imcivree Cost?**

At the maximum recommended dose in pediatric patients aged 17 or younger, treatment with Imcivree is expected to cost \$294,172 per patient per year. In adults aged 18 years and older, treatment is expected to cost \$441,258 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that setmelanotide be reimbursed for weight management in adult and pediatric patients aged 6 years and older who have obesity due to BBS only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

BBS is a rare genetic disease and highly heterogeneous ciliopathy that impacts multiple body systems. Hyperphagia associated with obesity is considered a hallmark in patients with BBS, and it is thought to be caused by the impairment of the melanocortin-4 receptor (MC4R) pathway, which can affect satiety, appetite regulation, food intake, and energy expenditure. CDEC recognized that setmelanotide, an MC4R agonist, is the only available therapy that targets the underlying disease mechanism of BBS.

One phase III study with a 14-week, randomized, double-blind, placebo-controlled period followed by a 52-week, open-label, single-arm period demonstrated that treatment with setmelanotide resulted in added clinical benefit in patients aged 6 years or older with BBS and obesity. Study 023 enrolled patients with BBS (N = 44) or Alström syndrome (AS) (N = 8) and obesity, although only the BBS population is relevant to this recommendation, and BBS-specific subgroup results were provided as a post hoc analysis. Among patients with BBS, Study 023 demonstrated that treatment with setmelanotide for 52 weeks resulted in a clinically meaningful reduction in weight-related parameters, such as total body weight and BMI, and the results were supported by the exploratory comparative 14-week placebo-controlled outcomes. The results also suggested a consistent reduction in hunger score in patients without cognitive impairment in both the placebo-controlled period and open-label period, but the scale used to measure hunger has not been externally validated; therefore, it is inconclusive whether these results are clinically meaningful. Similarly, the results of the health-related quality of life (HRQoL) outcomes at 52 weeks appeared to support the beneficial effect, but small sample sizes and the single-arm study design made it challenging to attribute these results to setmelanotide.

Patients identified a need for targeted treatments to reduce and manage the unrelenting hunger and resulting obesity caused by BBS. Although there are other unmet needs in the treatment of BBS, unrelenting hunger, hyperphagia, and obesity were identified by patient groups as some of the most common and distressing symptoms of BBS. CDEC concluded that patients who received setmelanotide experienced clinically meaningful reductions in total body weight or BMI, and that it may address unmet needs related to hunger. CDEC recognized that there is significant unmet need for patients with BBS as it is a rare, incurable genetic disease for which no targeted treatments are available and that setmelanotide might address some of these important unmet needs.

Using the sponsor-submitted price for setmelanotide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for setmelanotide was \$2,336,431 and \$2,726,591 per quality-adjusted life-year (QALY) gained compared with best supportive care when initiated in pediatric or adult patients,

respectively. At these incremental cost-effectiveness ratios, setmelanotide is not cost-effective at a \$50,000 per QALY willingness to pay threshold for weight management in patients 6 years of age or older with obesity due to BBS. A price reduction is required for setmelanotide to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Treatment with setmelanotide should be reimbursed when initiated in patients aged 6 years and older with clinically or genetically confirmed BBS and obesity.	Study 023 enrolled patients who were at least 6 years old, had obesity, and had a clinical diagnosis of BBS. Patients were not required to have genetically confirmed their diagnoses.	In Study 023, obesity was defined as BMI $\geq$ 30 for patients aged $\geq$ 16 years, or weight > 97th percentile for age and sex in patients aged < 16 years.  In Study 023, genetically confirmed BBS was defined as homozygous or compound heterozygous loss-of-function mutation in BBS genes.  In Study 023, clinical diagnosis of BBS was based on Beales criteria.
2. The maximum duration of initial authorization is 26 weeks.	Although the duration of setmelanotide treatment in Study 023 was 52 weeks, the product monograph approved by Health Canada notes that if a patient has not achieved clinically meaningful weight loss by 22 weeks, it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. CDEC recommended that initial authorization be 26 weeks to provide 4 weeks of additional flexibility to accommodate scheduling of follow-up evaluations.	—
<b>Renewal</b>		
3. For renewal after initial authorization, the physician must document the beneficial clinical effect when requesting continuation of reimbursement, including: <ol style="list-style-type: none"> <li>3.1. at least a 5% reduction in BMI or total body weight in patients who are at least 12 years of age, or</li> <li>3.2. a reduction in BMI Z score that is considered clinically beneficial by the treating physician as appropriate for</li> </ol>	A 5% reduction in total body weight or BMI was agreed by clinical experts to be clinically meaningful in the management of obesity in patients with BBS. The product monograph noted that if after 22 weeks of treatment a patient has not lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential, discontinue setmelanotide as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.  Metrics of improvement in body weight change become confounded in growing children. In Study 023, BMI Z score was used for children aged 6 to < 12 and there was no established threshold for minimal response in BMI Z score.	The clinical experts noted to CDEC that although there are no specific clinically meaningful changes in BMI Z score developed regarding weight loss in patients with BBS, it is clinically plausible that the clinically meaningful changes in BMI Z score for weight loss in BBS would be the same as those for the general population, which is estimated to be at least a 0.20 reduction in BMI Z score in general pediatric obesity.

Reimbursement condition	Reason	Implementation guidance
patients who are 6 to 11 years of age.		
4. For subsequent renewal, the physician must provide proof that the initial response achieved after the first 26 weeks of therapy with setmelanotide has been maintained. Subsequent renewals should be assessed annually.	<p>Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.</p> <p>The clinical experts indicated to CDEC that weight loss is expected to plateau even with effective treatments, and maintenance of reduced weight is sufficient for subsequent renewals.</p>	<p>The clinical experts noted to CDEC that interpretation of “maintenance” of weight loss in children aged younger than 12 years and/or before or during puberty may be complex and case-by-case due to normal growth patterns.</p> <p>The clinical experts noted to CDEC that maintenance of weight-related metrics (total body weight, BMI, or BMI Z score) since initial renewal is considered to be beneficial when taking a long-term view of the natural history of obesity and its comorbidities in patients with BBS.</p>
<b>Prescribing</b>		
5. The patient must be under the care of an endocrinologist, pediatric endocrinologist, and/or specialist in weight management or obesity.	<p>Carefully considered diagnosis and follow-up of patients with BBS is important to ensure that setmelanotide is prescribed for the most appropriate patients, and that adverse effects are managed appropriately.</p> <p>The clinical experts indicated to CDEC that, ideally, an interdisciplinary team of specialist medical doctors, mental health supports, and registered dietitians should be overseeing the care of patients with BBS. Access to some specialists or supports may be challenging based on geographic location and other circumstances.</p>	—
<b>Pricing</b>		
6. A reduction in price	<p>When initiated in pediatric patients, the ICER for setmelanotide is \$2,336,431 per QALY gained when compared with BSC. When initiated in adults, the ICER is slightly higher at \$2,726,591 per QALY gained versus BSC.</p> <p>A price reduction of 98% would be required for setmelanotide to achieve an ICER of \$50,000 per QALY compared to BSC.</p>	—
<b>Feasibility of adoption</b>		
7. The feasibility of adoption of setmelanotide must be addressed.	<p>At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor’s estimate and CADTH’s estimate.</p>	—

BBS = Bardet-Biedl Syndrome; BMI = body mass index; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

## Discussion Points

- CDEC considered the rarity and severity of the condition, patient population, and the lack of therapeutic options available, all of which represent a significant unmet need for this population. Early onset obesity and hunger or hyperphagia (and related behaviours and HRQoL impacts) have been identified by patient and clinician input as 2 of the most distressing features of BBS.
- The clinical experts noted to CDEC that setmelanotide is considered the most clinically appropriate first-line therapy for patients with BBS who have hyperphagia and obesity because it is the only available therapy that targets the underlying disease mechanism of BBS. It was also noted that there is a lack of data for other pharmacological therapies in the treatment of BBS outside of very few case studies. CDEC discussed that behaviour modification, intensive dietary regimens, and exercise should be considered in combination with setmelanotide as first-line treatment. Notably, these nonpharmacological interventions are particularly challenging in this population due to the biologically driven hyperphagia, high prevalence of cognitive impairment and other comorbidities, and early-age onset of the disease. As such, it is considered inappropriate to withhold or delay pharmacological treatment to trial behaviour and lifestyle modifications alone.
- Input from clinician and patient groups indicated that hyperphagia is 1 of the most distressing symptoms of BBS and represents an important unmet need. In Study 023, although there appeared to be an improvement in hunger at 52 weeks and in comparison to placebo at 14 weeks, the hunger questionnaires developed by the sponsor and the associated minimal important differences (MIDs) have not been externally validated. It is therefore inconclusive whether the observed benefits in hunger scores are clinically meaningful and whether they can be interpreted as attributable to setmelanotide. CDEC discussed that, while controlling hyperphagia is an important unmet need, there is currently no validated questionnaire to appropriately measure treatment effect on hyperphagia.
- The clinical experts noted to CDEC that clinical diagnosis is typically based on the Beales criteria. As BBS is a genetic ciliopathy that causes multisystem manifestations, clinical misdiagnosis is unlikely, although diagnosis may be delayed by the rarity of the disease and resulting lack of familiarity, progressive development of symptoms in childhood, and stigma around obesity and hyperphagia.
- CDEC discussed the diversity of opinion on requiring genetic confirmation for treatment eligibility. It was also noted that the group of genes identified is probably incomplete, and there are other mutations causing MC4R pathway clinical disorders that have yet to be identified. Reliance on the list may not be appropriate. Hence, CDEC recommended that before initiating treatment with setmelanotide, patients have to have a diagnosis of BBS confirmed either clinically or genetically. The clinical experts noted to CDEC that the majority of patients with clinically suspected BBS do seek genetic testing, which is provided as an out-of-country test. Given the limited availability of genetic testing to confirm a BBS diagnosis and the cost burden that their implementation would place on public health care systems, CDEC recommends that the sponsor be required to cover the cost of these tests across Canada, as well as to ensure their availability where needed.

- CDEC discussed that there are uncertainties regarding the long-term efficacy and safety of setmelanotide given that it may be a potentially life-long treatment, and the long-term extension study (Study 022) was still ongoing at the time of review.
- CDEC discussed ethical and equity considerations related to setmelanotide, including those related to the significant physical, emotional, and psychosocial burden of living with, or providing care to someone living with, BBS. CDEC also discussed how the patient population may be considered particularly vulnerable given that onset of BBS and its diagnosis typically occurs in early childhood and some patients may also be living with cognitive impairment. While there is limited evidence regarding the long-term efficacy and safety of setmelanotide, CDEC also discussed how setmelanotide could meet significant unmet need for people living with BBS, were it reimbursed. The committee discussed the importance of weighing the potential harms of requiring confirmatory genetic testing in addition to a clinical diagnosis for prescribing setmelanotide (e.g., may pose potential barrier to access) against the potential benefits (e.g., may prevent indication creep, especially recognizing the high cost of the drug). Relatedly, the committee discussed potential geographic disparities in access to the specialized care required to receive both a diagnosis and setmelanotide. CDEC discussed the need for continued collection of long-term data to inform clinical and policy decision-making, such as through the creation of a Canadian-based patient registry to better understand the safety and efficacy of setmelanotide in the heterogeneous patient population in Canada and to mitigate potential ethical concerns, including related to privacy, that might arise when sharing data in international patient registries.

## Background

BBS is a rare genetic disease and highly heterogeneous ciliopathy that impacts multiple body systems. Patients may have many symptoms such as retinal degeneration, obesity, renal anomalies, polydactyly, hypogonadism, and intellectual impairments. Hyperphagia associated with obesity is considered a hallmark in patients with BBS, and it is thought to be caused by the impairment of the MC4R pathway, which can affect satiety, appetite regulation, food intake, and energy expenditure. Excessive food-seeking behaviour negatively impacts the lives of patients and caregivers, posing difficulties with productivity and concentration at work and school, affecting their emotional and psychosocial status, and impairing relationships and quality of life. Additionally, early onset obesity can increase the risk of obesity-related morbidities such as cardiometabolic diseases, liver disease, and diabetes. The prevalence of BBS is estimated to be 1 in 100,000 to 160,000 in North America and Europe. Approximately 300 to 400 individuals in Canada have BBS, and the disorder occurs with greater frequency in certain populations of Newfoundland and Labrador (where there is a prevalence of 1 in 16,000 to 18,000). BBS can be diagnosed based on clinical features (e.g., retinal dystrophy, obesity, postaxial polydactyly) using Beales diagnostic criteria, which may be supported by out-of-country genetic testing.

As there are no targeted therapies for BBS, management of obesity uses the same approaches as for those in the general population, such as modifications of diet and lifestyle, but adherence to these practices and



sustainability of weight loss are especially low in this population due to the biologically driven hyperphagia and high prevalence of other BBS-related manifestations (e.g., visual or cognitive impairment). There are no Health Canada–approved treatments for obesity and control of hunger in patients with BBS, but some pharmacotherapies may be used off-label, such as glucagon-like peptide 1 receptor agonists (e.g., semaglutide injection or liraglutide injection) or gastrointestinal lipase inhibitors (e.g., orlistat), which are each reimbursed in some Canadian jurisdictions for adults with type 2 diabetes (semaglutide) or in patients with obesity and 1 weight-related comorbid condition (e.g., liraglutide, orlistat). However, there is no clinical evidence outside of very few case studies for the use of these therapies in BBS, and these therapies do not target the underlying mechanism of BBS.

Setmelanotide has been approved by Health Canada for weight management in adult and pediatric patients aged 6 years and older with obesity due to BBS. Setmelanotide is an MC4R agonist that is available as a 10 mg/mL solution in a 1 mL multiple-dose vial, administered via once daily subcutaneous injection; the dosage recommended in the product monograph is up to 3.0 mg daily in patients aged 18 years or older or up to 2.0 mg daily in patients aged 6 to 17 years.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III 14-week randomized controlled trial and 52-week open-label clinical study in BBS and AS, with subgroup data for the BBS population
- patients perspectives gathered by 1 patient group, the Bardet Biedl Syndrome Foundation
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with BBS
- input from 1 clinician group, The Canadian Endocrinologists Treating BBS
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to setmelanotide.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from the clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

CADTH received 1 input from the Bardet Biedl Syndrome Foundation, which conducted an online survey and one-on-one telephone or video conference interviews. The majority of the survey respondents were from the US (61%).

According to the patient input, 71% of patient and caregiver respondents indicated that they or their loved ones currently live with obesity. Patients with BBS constantly think of food and take a longer time to feel full after eating. According to the input, BBS-related obesity and BBS-related hunger impact the emotional and psychological well-being of patients, their social lives, and their work or school lives.

The patient input stated that there is no approved treatment for BBS or BBS-related hunger and obesity in Canada. Patients were reported to be using environmental factors such as exercise, supervision from others, calorie-restricted diets, and adhering to meals as somewhat to very effective measures for weight management. However, caregiver respondents noted that these strategies are challenging to implement. Patient and caregiver respondents identified not thinking about food constantly, not feeling hungry right after eating, and reducing stigma and/or judgment and stress as key outcomes for treatment of BBS-related hunger.

Two patient and 2 caregiver respondents from the patient input group indicated that they or their loved ones had experience with some off-label weight management medications such as semaglutide and phentermine, with 1 of these respondents noting that semaglutide was being used at the same time as setmelanotide. The respondents reported that these treatments were somewhat to very effective.

According to the patient input, 4 patient respondents and 13 caregiver respondents stated that they or their loved one had experience with setmelanotide and that the treatment had helped with controlling appetite and hunger, managing weight, and improving quality of life. Interviews with 1 patient and 4 caregivers who had experience with setmelanotide were also provided in the patient input; comments were consistent with the survey input in terms of disease symptoms, improved outcomes, and recommendation that the drug be available and accessible for all patients living with BBS.

## Clinician Input

### **Input From Clinical Experts Consulted by CADTH**

The information in this section is based on input received from a panel of 4 clinical specialists consulted by CADTH for the purpose of this review.

The clinical experts indicated that the primary unmet need is a lack of targeted treatment options for patients with BBS, which is a very rare genetic ciliopathy that results in multisystem manifestations, commonly including early onset obesity and hyperphagia. The clinical experts indicated that lifestyle interventions for obesity management are particularly inefficient and unsustainable in this population because of biologically driven hyperphagia and other potential manifestations of BBS such as vision loss, behavioural issues, food-seeking behaviours, cognitive impairment, and others. The experts also highlighted that patients with early onset obesity due to BBS and hyperphagia may experience obesity for substantially longer than people with late onset common obesity, placing them at greater risk for downstream obesity-related comorbidities.

The clinical expert panel agreed that setmelanotide would be considered first-line therapy for patients with BBS who have hyperphagia and obesity, in combination with obesity management recommendations such as intensive diet and lifestyle changes. It was noted that setmelanotide would be the first available

therapy to target the underlying mechanism of BBS-associated hyperphagia, and that setmelanotide would not be expected to have an impact on manifestations in other body systems (e.g., ocular manifestations). The experts described that despite a lack of data, combination therapy of setmelanotide and glucagon-like peptide 1 receptor agonists was likely to occur in some circumstances, including for those with the comorbidity of BBS with type 2 diabetes. The experts noted that there is some evidence that the response to bariatric surgery may be less durable in populations with hyperphagic obesity, and that there is no data for any other pharmacotherapies in the treatment of patients with BBS.

The experts indicated that genetic testing for the suite of known BBS mutations is currently not available in Canada but is requested through the provincial ministries of health as an out-of-country test and does not cause out-of-pocket expense for the patients. Clinical diagnosis using the Beales criteria was considered common and sufficient, and that misdiagnosis was unlikely, but the experts noted that the majority of patients also seek genetic confirmation. There was a diversity of opinion among the clinical experts on whether genetic testing should be a requirement before receiving BBS-targeted therapies because there may be currently unknown BBS-causing mutations.

The clinical experts indicated that it is not currently known which patients are the most or least likely to demonstrate a clinically meaningful response to treatment with setmelanotide, but it is clinically plausible that differences in the underlying mutation may be relevant for prognosis and treatment effect, and more data are needed in this area. In terms of assessing response, the experts indicated that a 1-year trial period was reasonable and a meaningful response would be a qualitative improvement in hunger and/or HRQoL, and a reduction of 5% or more in body weight in adults or 5% or more in BMI in pediatric patients. There were variable opinions on approaches to treatment if a patient did not achieve a 5% or more weight loss. In 1 approach, setmelanotide would be discontinued; in another approach, continuing on setmelanotide would be considered if there were other positive changes; combination therapy may be considered. Other discontinuation criteria may include severe adverse events (AEs) that cannot be managed by dose reductions or pausing the medication, if there is no impact on hyperphagia after 12 months of treatment, or when there are significant issues with nonadherence. The clinical experts also noted that patient registries for BBS would be of great value as there are still evidence gaps, especially regarding long-term efficacy and safety, given that obesity is a chronic, long-term, relapsing condition.

### **Clinician Group Input**

One clinician group input was received from Canadian Endocrinologists Treating BBS. Overall, the input was aligned with the clinical experts consulted by CADTH.

The clinician group reported that BBS is characterized by multisystem manifestations such as early onset obesity with hyperphagia and related complications, intellectual and cognitive impairment, delayed development, renal anomalies, polydactyly, retinal dystrophy, hypogonadism, and hypogonitalism. The input stated that around 72% to 92% of patients with BBS have obesity and hyperphagia caused by hypothalamic dysfunction leading to reduced MC4R activation. The clinician group commented that obesity is recognized as a complex, chronic, progressive, and relapsing condition.

The clinician group input stated that no targeted therapy exists for the treatment of BBS; the disease is managed symptomatically in a similar manner to the general population. The clinician group input indicated that hyperphagia is considered the most distressing symptom associated with BBS and that it is associated with many negative effects on the quality of life and physical and mental health of patients with BBS and obesity. The input stated that some environmental control and lifestyle interventions, such as food supervision, energy intake reduction, and meal schedules, that are used to manage obesity are challenging to implement and not sustainable as they do not address persistent hyperphagia. In addition to that, other symptoms associated with BBS, such as vision impairment, lack of balance or coordination, and intellectual disabilities, could make the implementation of these interventions more complicated.

The input noted that some procedures such as bariatric surgery and off-label therapies like liraglutide, semaglutide, and naltrexone-bupropion have no evidence of safety and effectiveness in patients living with BBS as these options do not address the biologically driven hyperphagia.

The clinician group indicated that obesity management goals should consider the prevention of morbidity associated with obesity, including but not limited to cardiometabolic disease, diabetes, liver diseases, and sleep apnea (this perspective aligned with the clinical experts consulted by CADTH).

The input suggested that setmelanotide could serve as an additional treatment option in the therapy plan, along with lifestyle and environmental interventions, to address obesity in patients with genetically confirmed BBS who are aged 6 years or older. The clinician group input indicated that treatment response would be assessed after 12 to 16 weeks of therapy. The input agreed that discontinuation should be considered if a decrease of 5% or greater in weight or baseline BMI has not been achieved, also during pregnancy and/or breastfeeding, lack of response, presence of side effects, renal impairment, and contraindication to setmelanotide. The clinician group inputs reported that a holistic multidisciplinary approach is required to care for patients with BBS.

### Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for setmelanotide:

- relevant comparators
- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
<p>The comparator in the submitted trial was placebo, so there is no evidence comparing setmelanotide with other medications for weight loss.</p> <p>Is it possible other medications for weight loss (e.g., liraglutide, semaglutide, naltrexone-bupropion combination, orlistat) would have been more appropriate comparators than placebo?</p> <p>Public drug plans do not generally fund the previously noted drugs for weight loss. An exception is that orlistat is funded for obesity by the Canadian Armed Forces.</p>	<p>CDEC and the clinical experts agreed that placebo is the most relevant comparator for weight loss in patients with BBS because there are no other pharmacotherapies currently studied for the treatment of this specific population, and setmelanotide is the first therapy that directly addresses the underlying cause of hyperphagia and obesity in BBS. There is no evidence available outside of case reports for the efficacy of other appetite-reducing drugs such as semaglutide 2.4 mg in patients with BBS; additionally, semaglutide 2.4 mg is only approved for adults (age ≥ 18 years) in Canada, while the approval for an indication for adolescents aged 12 years and older is pending.</p>
<b>Considerations for the initiation of therapy</b>	
<p>The patients included in the pivotal trial had a clinical diagnosis of BBS.</p> <p>Should patients require genetic (or other) testing to confirm BBS? If so, is such testing routinely available?</p>	<p>The experts noted that although the majority of patients do pursue genetic confirmation of diagnosis, more BBS mutations may yet be discovered. As a result, there is a diversity of expert opinion on whether genetic testing should be required before treatment. In 1 approach, it is considered inappropriate to require genetic testing before accessing targeted therapies for BBS due to the possibility of currently unknown mutations. In another approach, genetic testing is always sought and is appropriate to confirm diagnosis of BBS.</p> <p>There is no genetic test available in Canada that includes all currently known BBS-causing mutations, and this test is commonly covered by the MOH by special application as an out-of-country test. [REDACTED]</p> <p>As BBS is a genetic ciliopathy that causes multisystem manifestations, clinical misdiagnosis is unlikely, although diagnosis may be delayed by the rarity of the disease and resulting lack of familiarity, progressive development of symptoms in childhood, and stigma around obesity and hyperphagia.</p> <p>CDEC recommended that a BBS diagnosis be confirmed either genetically or clinically based on the Beales criteria. CDEC also recommended that the sponsor be required to cover the cost of the genetic testing across Canada and to ensure its availability where needed.</p>
<p>The exclusion criteria for the pivotal trial included:</p> <ul style="list-style-type: none"> <li>• recent (within 2 months) intensive diet and/or exercise resulting in &gt; 2% weight reduction</li> <li>• use of approved obesity medication within 3 months of randomization</li> <li>• prior gastric bypass resulting in &gt; 10% weight reduction durably maintained.</li> </ul> <p>Given the cost of setmelanotide, should patients be required to have insufficient clinical response to other interventions before access to therapy is provided?</p>	<p>CDEC and the experts agreed that setmelanotide is considered the most clinically appropriate first-line therapy for patients with BBS who have hyperphagia and obesity because it is the only available therapy that targets the underlying disease mechanism of BBS. There is also a lack of data for other pharmacological therapies in the treatment of BBS outside of very few case studies.</p> <p>CDEC and the experts agreed that behaviour modification, intensive dietary regimens, and exercise should be considered in combination with setmelanotide as first-line treatment. Notably, these nonpharmacological interventions are particularly challenging in this population due to biologically driven hyperphagia, the high prevalence of cognitive impairment and other comorbidities, and the early-age</p>

Implementation issues	Response
	<p>onset of the disease. As such, it is considered inappropriate to withhold or delay pharmacological treatment to trial behaviour and lifestyle modifications alone.</p>
<b>Considerations for discontinuation of therapy</b>	
<p>The sponsor noted that a 10% reduction in body weight from baseline is clinically meaningful.</p> <p>The sponsor also noted that “if an adult patient has not lost <math>\geq 5\%</math> of baseline body weight, or <math>\geq 5\%</math> of baseline BMI for patients aged less than 18 years, setmelanotide treatment should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.”</p> <p>How should clinically meaningful weight loss be defined? What duration of treatment is appropriate for assessing response to therapy?</p>	<p>The clinical experts noted that a 1-year trial period is reasonable for determining whether a patient is responding to setmelanotide.</p> <p>Meaningful response in the 1-year trial period would be a qualitative improvement in hunger and/or HRQoL, and a reduction of <math>\geq 5\%</math> in body weight in adults (<math>\geq 16</math> years old) or <math>\geq 5\%</math> in BMI in pediatric patients (<math>&lt; 16</math> years old). However, the measures of hunger and HRQoL are subjective and the approaches must differ by age of patient and by the presence or absence of cognitive impairment. Lack of improvement in hyperphagia after 1 year of treatment would trigger consideration of discontinuing therapy.</p> <p>Additionally, clinical expert opinion differs as to whether setmelanotide should be discontinued if the threshold of a <math>\geq 5\%</math> reduction in weight or BMI has not been achieved after 1 year of treatment. In the opinion of some clinical experts, maintenance of weight instead of persistent weight gain is still an indicator of treatment response in circumstances where the patient would have otherwise been gaining weight if untreated, and if there are other benefits observed after 1 year, such as reduction in hyperphagia, improvement in HRQoL, and improvement in markers of metabolic health. Additionally, some experts expressed that continuation of setmelanotide and additional lifestyle changes and/or combination pharmacotherapy could be considered on a case-by-case basis.</p> <p>It is worth noting that the Health Canada–approved product monograph recommends that in patients with BBS, evaluation of weight loss should occur after 22 weeks of treatment with setmelanotide. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for patients with continued growth potential, discontinuation is recommended as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.</p> <p>CDEC recommended that the maximum duration of initial authorization is 26 weeks and that for renewal after initial authorization, the physician must document the beneficial clinical effect when requesting continuation of reimbursement, including a 5% reduction in BMI or total body weight in patients who are at least 12 years of age; or, a reduction in BMI Z score that is considered clinically beneficial by the treating physician as appropriate for patients who are aged 6 to 11 years.</p>
<b>Considerations for prescribing of therapy</b>	
<p>Which specialists should be responsible for overseeing therapy with setmelanotide? Are such specialists widely accessible?</p>	<p>CDEC and the experts agreed that the most common prescribing physicians for setmelanotide would likely be endocrinologists or pediatric endocrinologists but may also include specialists in weight management. Ideally, an interdisciplinary team of specialist medical doctors, mental health supports, and registered dietitians should be overseeing the care of patients with BBS. Access to some specialists or supports may be challenging based on geographic location and other</p>

Implementation issues	Response
	circumstances. Remote consultation technology may be an appropriate means to increase access where necessary.

BBS = Bardet-Biedl Syndrome; BMI = body mass index; CDEC = CADTH Canadian Drug Expert Committee; HRQoL = health-related quality of life; MOH = Ministry of Health.

## Clinical Evidence

### Pivotal Studies and RCT Evidence

#### Description of Studies

Study 023 was a phase III, open-label trial with a 14-week randomized double-blind placebo-controlled period followed by a 52-week open-label period that aimed to evaluate the efficacy and safety of setmelanotide (1 mg to 3 mg daily by subcutaneous injection) in patients aged 6 years or older with BBS or AS and obesity. For the purposes of this review, only the patients with BBS were of interest, and results from this subgroup of patients were provided in a post hoc analysis. Patients were also divided into “pivotal” and “supplemental” cohorts, wherein patients in the pivotal cohort were defined as all patients enrolled up to the sixth patient with AS, which included 32 patients with BBS and 6 patients with AS. The patients in the supplementary cohort (12 patients with BBS and 2 with AS) were included in some secondary and all safety outcomes. Outcomes assessed at 52 weeks of setmelanotide treatment, such as the primary and key secondary outcomes, were measured from the “active treatment baseline” as opposed to the true baseline of the study, which would be after week 14 for patients who were initially randomized to placebo, so that patients would have approximately 52 weeks of active treatment experience for single-arm outcomes. In contrast, outcomes assessed during the first 14 weeks as placebo-controlled outcomes were measured from the “placebo-controlled baseline” (i.e., the true baseline of the study).

The primary outcome of Study 023 was the proportion of pivotal patients aged 12 years and older at baseline treated with setmelanotide for approximately 52 weeks who achieved a 10% or more reduction in body weight, measured from active treatment baseline. This single-arm outcome was compared against an external control, sourced from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS), in which 6.4% of adults with BBS were shown to achieve a 10% or more weight loss over a 1-year period on average. The CRIBBS data did not include any information regarding significant efforts to lose weight and reflects a heterogeneous real-world approach to BBS management. In Study 023, the prespecified threshold was rounded up from 6.4% to 10% of patients expected to achieve a 10% or more reduction in body weight without setmelanotide treatment.

Hunger scores were assessed as a key secondary outcome in patients ages 12 years or older without cognitive impairment using daily questionnaires developed by the sponsor, in which hunger was rated in terms of average daily hunger, morning hunger, and worst or most hunger over 24 hours, each on a scale of 0 to 10 wherein 10 represents the hungriest possible. Other secondary outcomes included placebo-controlled metrics of weight loss and hunger scores at 14 weeks, measured from a placebo-controlled baseline. Exploratory outcomes included change in waist circumference, change in fasting lipids, and change in

HRQoL [redacted] Impact of Weight on Quality of Life Lite [IWQoL-Lite], the Pediatric Quality of Life [PedsQL], and [redacted]), as well as safety.

At baseline, patients with BBS included 32 patients in the pivotal cohort and 12 in the supplemental cohort. Patients were mostly white (68.2% and 86.4% in the setmelanotide and placebo arms, respectively), with a mean age of 18.5 (standard deviation [SD] = 9.7) years and 21.5 (SD = 12.6) years, respectively. There was a high prevalence of cognitive impairment (54.5% and 36.4%, respectively). The mean BMI was 41.4 kg/m<sup>2</sup> (SD = 10.0) and 41.6 kg/m<sup>2</sup> (SD 10.1), respectively. Although genetic confirmation was not required, over 90% of patients had a genetic confirmation of BBS, which was defined as homozygous or compound heterozygous loss-of-function mutation in BBS genes. Of the 22 pivotal and supplemental patients with BBS assigned to setmelanotide, 4 were younger than 12 years of age and 12 were younger than 17 years of age; among the 22 assigned to placebo, 4 were younger than 12 years of age and 10 were younger than 17 years of age.

## **Efficacy Results**

### ***Body Weight Change After 52 Weeks of Setmelanotide Treatment***

Among pivotal patients aged 12 years and older with BBS (N = 28), 35.7% (95% confidence interval [CI], 18.6% to 55.9%) had a 10% or greater reduction in body weight from active treatment baseline after 52 weeks of treatment with setmelanotide, which was greater than the prespecified assumption of 10% of patients with BBS achieving a 10% or greater reduction in body weight without setmelanotide treatment. The mean change and percent change in weight among patients with BBS in the pivotal cohort (N = 28) were -7.24 kg (SD = 8.208) and -6.47 kg (SD = 6.970), respectively. Results were similar when patients with BBS from the supplemental cohort were also included.

As an ad hoc analysis in response to a request by CADTH to reflect the Health Canada recommendations, the sponsor also provided the estimated proportion of patients with BBS aged 12 years or older in the pivotal cohort who achieved a 5% or greater reduction in total body weight after [redacted]

### ***Change in Hunger Scores After 52 Weeks of Setmelanotide Treatment***

Among patients with BBS in the pivotal cohort who were aged 12 years or older and had no cognitive impairment (N = 14), the mean percent change in hunger score after 52 weeks of setmelanotide treatment was -31.80% (95% CI, -48.81% to -14.79%). Of these patients, 71.4% experienced at least 1-point reduction ( $\geq 10\%$ ) and 42.9% of patients experienced at least 2-point reduction ( $\geq 20\%$ ) in the most-worst hunger score. Additionally, 57.1% experienced at least a 25% improvement in the weekly average of the 3 evaluated hunger scores (most-worst score over 24 hours, average score over 24 hours, or morning hunger score). The results were similar when patients with BBS from the supplemental cohort were also included. There is no known MID for these hunger scores.

### ***Body Weight Change After 14 Weeks of Setmelanotide Treatment Compared to Placebo***

In the placebo-controlled analysis of patients from the pivotal cohort aged 12 years or older with BBS, patients receiving setmelanotide (N = 14) had a greater mean percent body weight change (-3.31%; SD = 4.474%) than patients receiving placebo (N = 15; -0.25%; SD = 2.353%). The difference in mean percent



change was  $-2.96\%$  (95% CI,  $-5.65\%$  to  $-0.26\%$ ). Similar results were observed when considering both cohorts of patients with BBS.

### ***Change in Hunger Scores After 14 Weeks of Setmelanotide Treatment Compared to Placebo***

Among patients with BBS in the pivotal cohort who were aged 12 years or older and did not have cognitive impairment, those treated with setmelanotide (N = 5) had a greater reduction in hunger score than those treated with placebo (N = 9) in the mean change in average daily hunger score and most-worst hunger score from placebo-controlled baseline to week 14. However, the sample sizes were small and the 95% CI of the difference was very wide and included the null value in the cases of the percent change in hunger over 24 hours, mean change in morning hunger, and percent change in morning hunger. The results were similar when considering both cohorts of patients with BBS.

### ***Subgroup Analyses of Change in Body Weight and Hunger Scores***

There were 8 patients younger than 12 years of age with BBS in Study 023. All 8 patients with BBS had decreases of [REDACTED]. When including all patients aged 6 or older to younger than 12 with either AS or BBS (n = 11), during the 14-week placebo-controlled period, patients treated with setmelanotide (n = 6) had [REDACTED] (n = 5) in the same age group.

The subgroup results were directionally consistent among other age-specific subgroups of patients with BBS, including patients aged younger than 18 years and those ages 18 years or older.

Hunger was also assessed in patients with cognitive impairment by caregiver assessment using the [REDACTED] because there is no validated hunger assessment for this population, and patients with [REDACTED] share the symptoms of early obesity, intense hunger, and cognitive impairment. The scale ranges from 0 to 30, with higher scores indicating more severe hyperphagia-related behaviours. The mean change from active treatment baseline in 11 assessed patients was [REDACTED].

### ***Health-Related Quality of Life***

Exploratory HRQoL outcomes based on the IWQoL-Lite (patients aged  $\geq 18$  years; n = 11) and PedsQL (patients from the pivotal cohort aged  $< 18$  years; n = 9) generally showed improvement from active treatment baseline to week 52 of setmelanotide treatment; the mean change in IWQoL-Lite was  $+11.75$  (SD = 10.297), and the mean change in PedsQL was  $+11.2$  (SD = 14.4). Although no MIDs have been identified specifically in populations with BBS for either scale, a general population survey of children identified MIDs for PedsQL as 4.4 (self-report) or 4.5 (parent proxy report), and MIDs using IWQoL-Lite in patients with general obesity range from 7.7 to 12 points.

Some assessed patients had impaired HRQoL at baseline according to the IWQoL-Lite (n = 8/11) and PedsQL (n = 4/9), and the majority of these patients experienced improvement in scores after 52 weeks of setmelanotide treatment.

The results of the [REDACTED] in patients in the pivotal cohort who were aged 16 years or older and did not have cognitive impairment (n = 13) differed by health state score: improvements were seen in [REDACTED].

[REDACTED] were identified specific to BBS, obesity, or hyperphagia.

### **Harms Results**

The harms results discussed here are based on the safety analysis set (N = 57), which includes patients with BBS or AS, to maximize sample size. The results were similar in the BBS-only subgroup. The sponsor and clinical experts identified a number of AEs of special interest: injection-site reactions, anaphylaxis, bradycardia, hyperpigmentation, melanoma, sexual events, sexually inappropriate behaviours, and select psychiatric events, including anxiety, depression or depressed mood, suicidal ideation, suicide attempts, and aggression.

#### *Common Treatment-Emergent AEs and Serious AEs*

The most common treatment-emergent AEs experienced by patients were injection-site reactions (e.g., erythema, pruritus, bruising, induration, pain), skin hyperpigmentation, nausea, vomiting, and diarrhea.

Incidence of injection-site reactions, diarrhea, and nausea were similar between treatment arms during the placebo-controlled period, but vomiting was only experienced by patients treated with setmelanotide (n = 7; 25.9%). Incidents of vomiting also occurred in patients initially randomized to placebo when they later received setmelanotide (n = 7; 28.0%) during the open-label period, and tended to occur in the first month of setmelanotide treatment. No events of severe nausea or vomiting occurred.

Over the entire study, 100% of patients with BBS or AS experienced at least 1 AE and 3 patients (5.8%) experienced at least 1 serious AE. The serious AEs experienced over the entire study period included anemia, blindness, suicidal ideation, and anaphylactic reaction (as previously described in a patients treated with placebo), none of which were considered by the study investigators to be caused by the study drug.

#### *Discontinuation Due to AEs*

During the placebo-controlled period, 2 patients treated with setmelanotide and 3 patients treated with placebo discontinued treatment due to AEs. Of these, 1 patients treated with placebo and 1 patients treated with setmelanotide discontinued due to nausea and 1 patients treated with setmelanotide but none treated with placebo discontinued due to vomiting. In the setmelanotide treatment group, other AEs leading to discontinuation included 1 instance each of ocular hyperemia and face edema. In the placebo group, other AEs leading to discontinuation included 1 instance each of anaphylactic reaction, headache, acne, hidradenitis, and hot flush.

Over the entire study, [REDACTED] discontinued due to any treatment-emergent AE. The reasons for discontinuation over the entire 66-week study period (N = 57 with BBS or AS) included nausea (n = 3) and vomiting (n = 3), and 1 instance each of discontinuation due to ocular hyperemia, anaphylactic reaction, headache, acne, hidradenitis, hot flush, skin hyperpigmentation, and abdominal pain.

### ***AEs of Special Interest***

Hyperpigmentation was experienced frequently and exclusively in patients treated with setmelanotide (63.0% during the placebo-controlled period and 63.5% over the full study period). These events were expected because of the effect of melanocortin receptor agonism during setmelanotide treatment.

Sexual events occurred in some patients: [REDACTED]  
[REDACTED]  
[REDACTED] during the study period.

The other AEs of special interest were either [REDACTED]  
[REDACTED]

### ***Deaths***

No deaths occurred during the study.

### **Critical Appraisal**

Study 023 was a phase III, multicentre study and consisted of a 14-week, randomized, placebo-controlled, double-blind period followed by a 52-week, open-label, single-arm period. To reflect the requested reimbursement criteria, all efficacy outcomes considered in this report were post hoc reanalyses based on the subgroup of patients with BBS, who composed the majority of the overall population. The results of the post hoc analysis were consistent with the results of the prespecified analyses in the full analysis set. Although the population size was small, BBS is a rare disease with a small patient population, and the sample size exceeded the minimum power calculation conducted by the sponsor. However, the already small sample size was further restricted for hunger-related outcomes due to excluding patients with cognitive impairment, for exploratory outcomes related to HRQoL due to the different age requirements associated with the validated scales and the exclusion of patients with cognitive impairment, and across many outcomes due to missing data. There are inherent risks of bias, confounding, and uncertainty in the estimation of treatment effects from single-arm data due to unidentified, uncontrolled prognostic factors. Moreover, the open-label design of the single-arm period increases the risk of detection bias and performance bias, and may lead to overestimation of treatment effect for subjective outcomes. The duration of treatment for this period was considered appropriate by the clinical experts consulted by CADTH for evaluating weight loss and hunger, although longer-term data are also needed given that obesity in patients with BBS is a long-term, chronic, and relapsing condition.

The primary outcome of the proportion achieving a 10% or greater reduction in body weight at 52 weeks was considered to be conservative given that a 5% or greater reduction in body weight is widely accepted by clinical experts as clinically meaningful in patients with BBS and obesity. The trial result was compared to a prespecified threshold of 10% responders based on historical control data. The key secondary hunger-related outcomes were based on a hunger scale that has not been externally validated, which confounds interpretation of an MID; moreover, the results were compared against an assumption of no effect without treatment, which does not control for the possibility of the placebo effect and may be biased in favour of setmelanotide given that this is a subjective patient-reported outcome. The primary and key secondary

results from the 52-week analyses are supported by the exploratory placebo-controlled outcomes, in which at week 14, a higher percentage of patients in the setmelanotide treatment group had improvement in parameters related to weight loss and hunger compared to patients who received placebo.

The eligibility criteria and population characteristics at baseline were considered to be appropriate and generalizable to the population of interest (i.e., adult and pediatric patients with BBS, obesity, and hyperphagia who may or may not have cognitive impairment, and who may or may not have genetic confirmation of diagnosis). Although patients aged 6 years or older were included, most outcomes were analyzed in patients aged 12 years or older, and very few patients aged younger than 12 years were enrolled in the trial (n = 8). Additionally, although patients with cognitive impairment were enrolled, they were not included in the key secondary and exploratory outcomes related to hunger and HRQoL due to practical limitations of assessing these outcomes in those with cognitive impairment. Subgroup analyses of populations of younger people and those with cognitive impairment generally aligned with the primary and secondary outcomes described but interpretation of results was limited due to the small sample sizes. There are also concerns with generalizability to pediatric patients given that the average maintenance dose in pediatric patients in Study 023 (████████) exceeded the maximum recommended dose of 2 mg daily. The clinical experts consulted by CADTH indicated that dosing in real-world practice would mostly follow the product monograph, with occasional exceptions for patients who are older than 16 and may begin to receive adult dosing based on clinical judgment.

## Long-Term Extension Studies

### Description of Studies

Study 022 is an ongoing long-term extension that is a nonrandomized, open-label, single-arm study including patients aged 6 years and older with BBS and obesity. Enrolled patients were “responders” who completed 1 of the phase II or III studies (Study 014 or Study 023, respectively), demonstrated tolerability, and achieved a 10% or greater body weight reduction (patients ≥ 18 years old) or a 0.3 or greater reduction in BMI Z score (patients < 18 years old) after 52 weeks of setmelanotide treatment. Patients received personalized setmelanotide doses titrated to a target of 3 mg once daily. The primary objective was to evaluate safety and tolerability and the secondary objectives were to evaluate changes in weight and hunger.

### Efficacy Results

At the time of this review, Study 022 was still ongoing, and not all patients had completed the 36-month assessment. However, early findings from 12-month, 18-month, and 24-month assessments indicate that weight-related parameters tended to stabilize in ██████████ patients with BBS and obesity. ██████████

### Harm Results

During Study 022, 100% of patients experienced at least 1 treatment-related AE. The most common treatment-related AEs were injection-site reactions, skin hyperpigmentation, nausea, and vomiting. ██████████. No death related to AEs was reported. It was not reported whether deaths were observed in general.

## Critical Appraisal

The open-label design of Study 022 is considered a limitation that could increase the risk of detection bias and performance bias, and may lead to overestimation of treatment effect for subjective outcomes. The small sample size, immature data, lack of a control arm, and lack of adjustment for covariates are considered key constraints that limit the interpretation of the study's outcomes. Additionally, only a brief summary of the trial with limited reporting was available for this review. Hunger and HRQoL outcomes were also not reported.

## Indirect Comparisons

The sponsor conducted a feasibility assessment to determine if an indirect treatment comparison of setmelanotide versus 8 general obesity treatments, including semaglutide, lixisenatide, lisdexamfetamine, topiramate, liraglutide, naltrexone-bupropion, orlistat, and bariatric surgery can be undertaken. Systematic literature reviews were conducted to identify prospective or retrospective clinical studies, published or unpublished, pertaining to the treatment of patients with BBS and obesity. No relevant articles were identified in this patient population, so indirect comparisons were not feasible.

## Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered for this CADTH review, as well as relevant literature, were reviewed to identify ethical considerations relevant to the use of setmelanotide for the treatment of adult and pediatric patients aged 6 years or older with obesity due to BBS.

- Ethical considerations in the context of BBS highlighted the significant physical, emotional, and psychosocial burden of living with, and attending to, BBS (and, more specifically, BBS-related obesity and hyperphagia) for patients and their caregivers; diagnostic challenges due to the heterogeneous nature of BBS and the progressive onset of some of its clinical features (i.e., vision loss); challenges with coordinating the necessary multidisciplinary care for this multisystem condition; and unmet treatment needs for this population given the lack of any BBS-targeted treatment option and general reliance on lifestyle interventions.
- Clinical trial evidence regarding the effect of setmelanotide on weight, hyperphagia, and quality of life is generally supportive of improvements to patient outcomes, but there is uncertainty around the durability and magnitude of effect and safety that limits the ability to make definitive statements on the benefits, harms, or cost-effectiveness of setmelanotide.
- The use of setmelanotide presents potential risks for patients, including common risks of skin hyperpigmentation and vomiting, as well as possible sexual events, sexually aggressive behaviour, depression, suicidal ideation, and melanoma. However, given the current absence of any targeted treatment option for BBS-related obesity, as well as the potential benefits on weight management, hyperphagia, and common comorbidities of long-term obesity, clinicians and patients expressed a willingness to accept some risk. As such, if reimbursed, there will likely be a high uptake of setmelanotide in clinical practice and challenges around the appropriate eligibility and

discontinuation criteria will need to be navigated. Equitable access to setmelanotide will require addressing geographic barriers of access to specialist care and monitoring as well as the possibility that some patients with cognitive or vision impairment related to BBS may require additional support to fully access and achieve dose compliance with setmelanotide.

- Ethical considerations for health systems related to setmelanotide highlight the challenges of funding decisions and assessments of opportunity costs for expensive drugs for rare diseases. Given the uncertainty around the long-term safety and efficacy of setmelanotide, or whether some subtypes of patients respond better than others, work toward building this data to ensure better clinical decision-making and resource stewardship in the future may benefit from the development of a BBS-specific patient registry, which carries potential cost and infrastructural implications to current budgets.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	For adult and pediatric patients 6 years of age and older with impairments in the MC4R pathway due to genetic diseases, for the treatment of obesity and control of hunger for those with Bardet-Biedl syndrome
Treatment	Setmelanotide
Dose regimen	Adults (18 years and older): Initiate at 1 mg and titrate up by 0.5 mg per day every 2 weeks up to 3 mg once daily Pediatrics (17 years and younger): Initiate at 0.5 mg and titrate up by 0.5 mg per day every 2 weeks up to 2 mg once daily
Submitted price	\$402.70 per mg (10 mg/mL solution in a 1 mL multiple-dose vial)
Treatment cost	First year: \$411,559 (adults); \$276,252 (pediatrics) Subsequent years: \$441,258 (adults); \$294,172 (pediatrics)
Comparators	BSC alone: nutrition, exercise, and nonpharmacological interventions
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and LYs
Time horizon	Lifetime (85 years for pediatric-initiated patients, and 71 years for adult-initiated patients)
Key data source	Pivotal trial RM-493-023
Submitted results	Pediatric-initiated patients: \$1,185,599 per QALY gained (incremental costs = \$11,457,751; incremental QALYs = 9.66) Adult-initiated patients: \$1,288,761 per QALY gained (incremental costs = \$5,353,700; incremental QALYs = 4.15)

Component	Description
<p><b>Key limitations</b></p>	<ul style="list-style-type: none"> <li>• Hospitalization and specialist care visits that were dependent on a patient’s BMI but unrelated to obesity-related comorbidities were assumed to occur in the model. Based on clinical expert feedback obtained by CADTH, hospitalizations and specialty visits in the modelled population would be related to complications arising from obesity. Resource use associated with obesity was likely double counted in the analysis.</li> <li>• The utility values by BMI classes and age were obtained among patients who also had obesity-related comorbidities. The additional inclusion of obesity-related comorbidity disutilities likely double counted the quality of life impact associated with obesity.</li> <li>• The model used the same comorbidity prevalence rates (obtained from an older adult population) for all age groups (including pediatrics). This overestimated prevalence in younger age groups, especially for comorbidities such as osteoporosis and cardiovascular risk.</li> <li>• The utility value for severe hyperphagia was disparate from comparable literature estimates of hyperphagia. The sponsor also assumed all responders on setmelanotide transitioned to mild hyperphagia, which is counter to the trial data. This may have overestimated quality of life benefits of setmelanotide.</li> <li>• The model structure did not adequately assess the impact of weight loss on comorbidities or mortality.</li> <li>• The sponsor assumed setmelanotide would be discontinued among nonresponders with &lt; 10% weight loss at 52 weeks. The product monograph for setmelanotide recommends response be assessed at 22 weeks. The CADTH clinical experts noted that some clinicians may choose to continue treatment in patients with better hyperphagia control beyond 22 weeks.</li> <li>• The sponsor assumed that, on average, pediatric patients would receive a dose of [redacted]. Although this aligns with the clinical trial, the clinical experts consulted by CADTH noted that the maximum dose of 2 mg, per the product monograph, would likely be adhered to.</li> </ul>
<p><b>CADTH reanalysis results</b></p>	<ul style="list-style-type: none"> <li>• Changes to derive a CADTH base case included excluding hospitalization and specialty care visits unrelated to obesity-related comorbidities; excluding comorbidity disutility; using age-varying comorbidity prevalence rates; using alternate hyperphagia utilities from the literature; assuming a maximum pediatric dose of 2 mg per day; and using hyperphagia transition probabilities from trial.</li> <li>• In the CADTH base case, the ICER for setmelanotide compared to BSC was:             <ul style="list-style-type: none"> <li>◦ in pediatric-initiated patients: \$2,336,431 per QALY gained (incremental costs = \$10,425,770; incremental QALYs = 4.46)</li> <li>◦ in adult-initiated patients: \$2,726,591 per QALY gained (incremental costs = \$5,293,917; incremental QALYs = 1.94).</li> </ul> </li> <li>• CADTH notes outstanding limitations related to the model structure and inputs could not be resolved and these estimates likely overestimate QALY gains associated with setmelanotide.</li> </ul>

BMI = body mass index; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; MC4R = melanocortin-4 receptor; QALY = quality-adjusted life-year.

### Budget Impact

CADTH identified the following limitations with the sponsor’s analysis: the anticipated market uptake of setmelanotide is underestimated, there is uncertainty associated with the proportion of patients with BBS patients eligible for public coverage, there is uncertainty associated with the maintenance dose compliance rate, the funding of setmelanotide will not impact semaglutide use in this population, and patients discontinuing due to a lack of response is uncertain. Based on the CADTH reanalysis, the estimated budget impact from the reimbursement of setmelanotide would be \$4,679,772 in year 1, \$7,830,216 in year 2, \$10,859,642 in year 3, for a 3-year total of \$23,369,630.



## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

**Meeting date:** August 23, 2023

**Regrets:** None

**Conflicts of interest:** None





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