For your patients 2 years and older with obesity due to Bardet-Biedl syndrome (BBS)

Discover a Path Forward with IMCIVREE

Actor portrayals.

IMCIVREE is the **first and only PRECISION MEDICINE** to target impairment of the hypothalamic MC4R pathway, a root cause of hyperphagia and obesity due to BBS[1,2]

MC4R=melanocortin-4 receptor.

Indication

IMCIVREE is indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS).

Limitations of Use

IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- Other types of obesity not related to BBS or other FDA-approved indications for IMCIVREE, including obesity associated with other genetic syndromes and general (polygenic) obesity

Important Safety Information

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE®
(setmelanotide) injection

REFERENCES

NOT ALL OBESITY IS THE SAME: MC4R PATHWAY-DRIVEN OBESITY IS DIFFERENT FROM GENERAL OBESITY

Identifying the type of obesity your patient has can:

- Help you determine the optimal management of their specific disease[1,2]
- Reduce the cumulative impact of their obesity, especially if diagnosed early[3,4]

General obesity[5,6]

Occurrence: Can occur at any age, including later in life

Cause: Interaction of multiple factors, including:

- Age/race/gender
- Concurrent illnesses
- Common genetic variants
- Concomitant medications
- Environmental factors
- Nutrition and physical activity

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MC4R pathway-driven obesity[2,3,5,7]

Monogenic obesity	Syndromic obesity
LEPR, POMC, PCSK1 deficiencies	**Bardet-Biedl syndrome (BBS)**

Occurrence: Impairment is present at birth and leads to **hyperphagia** (insatiable hunger) and **early-onset obesity**

- May develop as early as a few months old; often appears in early childhood and continues into adolescence and adulthood

Cause: Rare genetic variants in the MC4R pathway, a signaling pathway in the hypothalamus

Understanding the role of the MC4R signaling pathway in obesity and hunger +

Knowing a root cause of your patient's hunger and early-onset obesity can be an important first step in making an accurate diagnosis which can lead to optimal management of their disease

MC4R=melanocortin-4 receptor; POMC=proopiomelanocortin.

REFERENCES

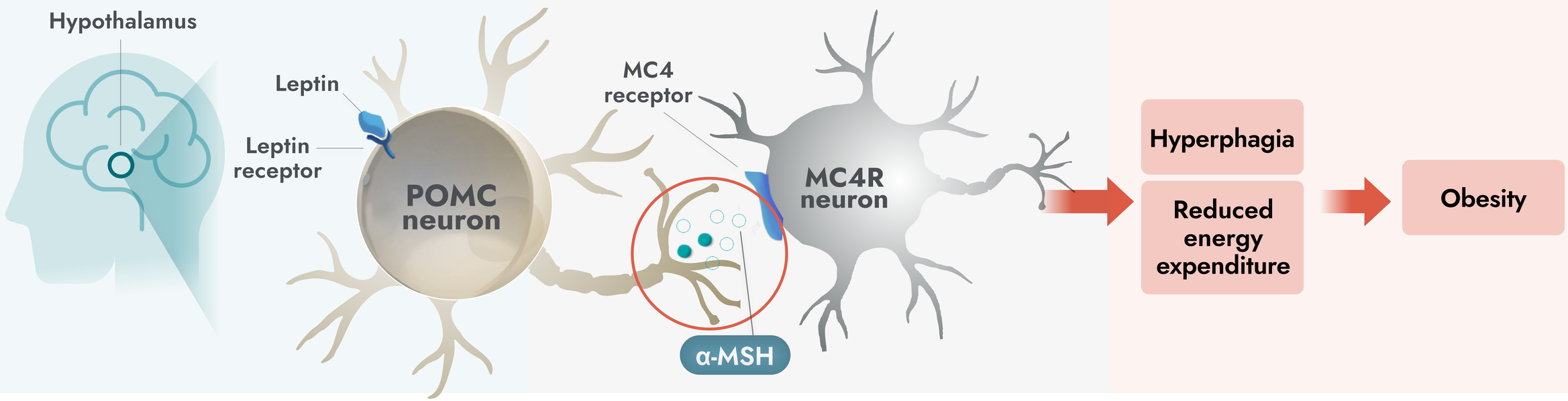
NOT ALL OBESITY IS THE SAME: MC4R PATHWAY-DRIVEN OBESITY IS DIFFERENT FROM GENERAL OBESITY

THE ROLE OF THE MC4R PATHWAY IN HYPERPHAGIA AND OBESITY[2,5,8,9]

A variant in one or more genes disrupts satiety signaling

Alpha-melanocyte-stimulating hormone (α-MSH) production is impaired or deficient, preventing activation of the MC4 receptor

Impairment of the MC4R pathway leads to decreased satiety signaling, hyperphagia, and reduced energy expenditure. This often leads to early-onset obesity



MC4R pathway impairment leads to hyperphagia and impacts your patient's weight trajectory[2]

Knowing a root cause of your patient's hunger and early-onset obesity can be an important first step in making an accurate diagnosis which can lead to optimal management of their disease

MC4R=melanocortin-4 receptor; POMC=proopiomelanocortin.

NOT ALL HUNGER IS THE SAME: HYPERPHAGIA IS A KEY SYMPTOM OF MC4R PATHWAY IMPAIRMENT

Identifying the type of hunger your patient has can help:
- Determine the underlying cause of your patient's hunger
- Lead to optimal management of their specific disease

Episodic/Periodic

Occasional overeating

Eating beyond a feeling of satiety at a special occasion or celebratory meal (eg, Thanksgiving)[10]

Hedonic overeating

Eating beyond satiety and metabolic needs, influenced by appetite and cravings[11,12]

Cause:
- The pleasure centers in the brain, often driven by emotion or environmental circumstances[11,12]

Binge eating

Episodic consumption of large amounts of food beyond hunger and/or satiety within a short period with a loss of control. If recurring, defined as Binge Eating Disorder (BED).[10,11]

Behaviors may include:
- Rapid eating[13]
- Eating in isolation[13]
- Distress due to eating behavior[4]

Cause:
- Psychological factors, family history, dieting, gender[3,11,13]

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Persistent

Hyperphagia caused by MC4R pathway impairment

Chronic, pathological, insatiable hunger and impaired satiety accompanied by persistent and abnormal food-seeking behaviors. Differentiated from other types of overeating by its severity and persistence.[3,14]

Main features/characteristics:
- Persistent preoccupation with food[3]
- Prolonged time to satiation and shortened duration of satiety[3]
- Prolonged feeling of hunger[3]
- Specific abnormal behaviors

Behaviors may include:
- Distress if food is unavailable
  - **Children:** may exhibit as tantrums or persistent negotiation/demand for food[14,15]
  - **Adults:** may manifest in emotional effects including sadness, frustration, irritability, anxiety, and/or guilt[16]
- Abnormal food-seeking behaviors such as night eating or hiding food (children may also steal/sneak food)[17]
- Eating excessively – not to be confused with binge eating

Symptoms and behaviors may range in severity[10]

Cause:
- Rare genetic variants in the MC4R pathway, a signaling pathway in the hypothalamus[2]

According to 2023 AAP and OMA guidelines, managing hyperphagia can be challenging and may require the use of pharmacotherapy[3,6]

REFERENCES

+ Caregiver quotes

+ Clinician quotes

If you have patients with hyperphagia and early-onset obesity, take a closer look to see if the patient has other symptoms of BBS

AAP=American Academy of Pediatrics; MC4R=melanocortin-4 receptor; OMA=Obesity Medicine Association.

Hyperphagia questionnaire ▶

CAREGIVER QUOTES

"The most challenging symptom (of BBS) was hyperphagia. We did not anticipate the severity of the hunger. It is much more intense and ever-present, and impacted everything we did. Even a joyful occasion like a birthday party was stressful. While all the kids were socializing, Reed was only concerned about food and not just concerned; he was infatuated with it."

— Kat, caregiver of a child living with BBS

"After her first birthday, we noticed a rapid weight gain, and she threw tantrums all the time and was very difficult to manage. Looking back, I see this was most likely due to how hungry she felt."

— Ann, caregiver of a child living with BBS

"While Wyatt and Carson have the same variants of the *BBS10* gene, only Wyatt has hyperphagia and obesity. I couldn't take both kids out by myself because Wyatt needed constant supervision to make sure he wasn't stealing food. I have to lock our fridge, trash, and pantry."

— Rachel, caregiver of a child living with BBS

Individual results may vary

Hyperphagia questionnaire

REFERENCES

CLINICIAN QUOTES

"I absolutely see varying degrees of hyperphagia, from extreme cases where patients have locks on cabinets and do not keep food in the home, to other less extreme cases where they've learned to adapt around it. I have one patient that has never admitted to having hyperphagia. In her words, sometimes she just suffers through it, or does other things, like drinks way too much water to try to feel full."

— Christy Davis, Obesity and Weight Management Specialist

"I had a parent say what he worried most about was not other health consequences, but the child's ability to learn. That resonated for me. All I could think was if my child is constantly thinking about food, how are they ever going to learn? It really drove it home for me."

— Uzoma Okorie, Pediatric Cardiologist

"I encourage clinicians to ask specific questions about how the feeling of hunger is impacting their patient's quality of life and ability to function in their life. Particularly around school, work, caregiving relationships, as well as around pleasure and fun. When you can see that hunger is negatively impacting or preoccupying all of those spaces, it is a really good cue they are experiencing hyperphagia. It needs to be high on our priority list of how we are going to help our patients, not only with their weight trajectories, but also with their hyperphagia."

— Alaina Vidmar, Pediatric Endocrinologist

Individual results may vary

REFERENCES

Hyperphagia questionnaire

REFER

Overview | Mechanism of Action | Study Design | Efficacy: Aged 2 to <6 | Efficacy: Aged 6 to <18 | Efficacy: Aged ≥18 | Safety Profile: Aged 2 to <6 | Safety Profile: Aged ≥6 | Dosing and Administration | Prescribing IMCIVREE | Rhythm InTune | Summary

THE MC4R PATHWAY IS A KEY SIGNALING PATHWAY IN THE HYPOTHALAMUS THAT REGULATES HUNGER AND ENERGY EXPENDITURE

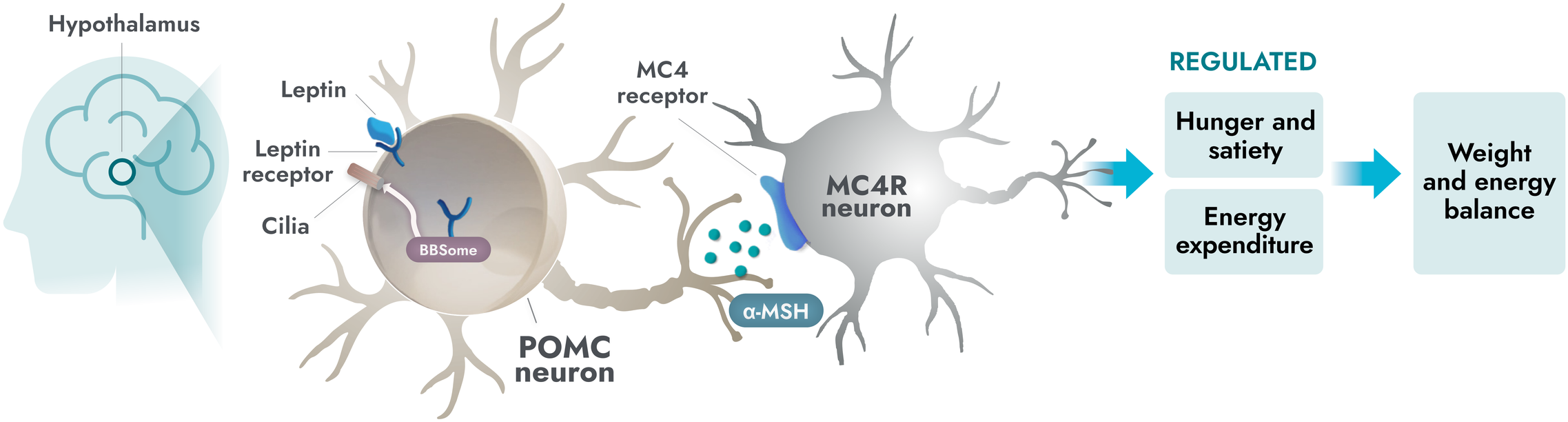
Functional MC4R pathway activity[2,5,8,9]

The **BBSome** plays a central role in **cilia** function, including trafficking of the **leptin** receptors (LEPR) to allow leptin activation and satiety signaling

Impaired MC4R pathway activity[2,5,8,9]

Leptin binding to LEPR triggers a signaling cascade, including secretion of alpha-melanocyte-stimulating hormone (α-MSH) from the POMC neuron. α-MSH binds to the MC4 receptor

Activation of the MC4R pathway regulates hunger and satiety, and energy expenditure, so weight and energy remain in balance



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BBSome
A complex of proteins formed by a host of *BBS* genes[19]

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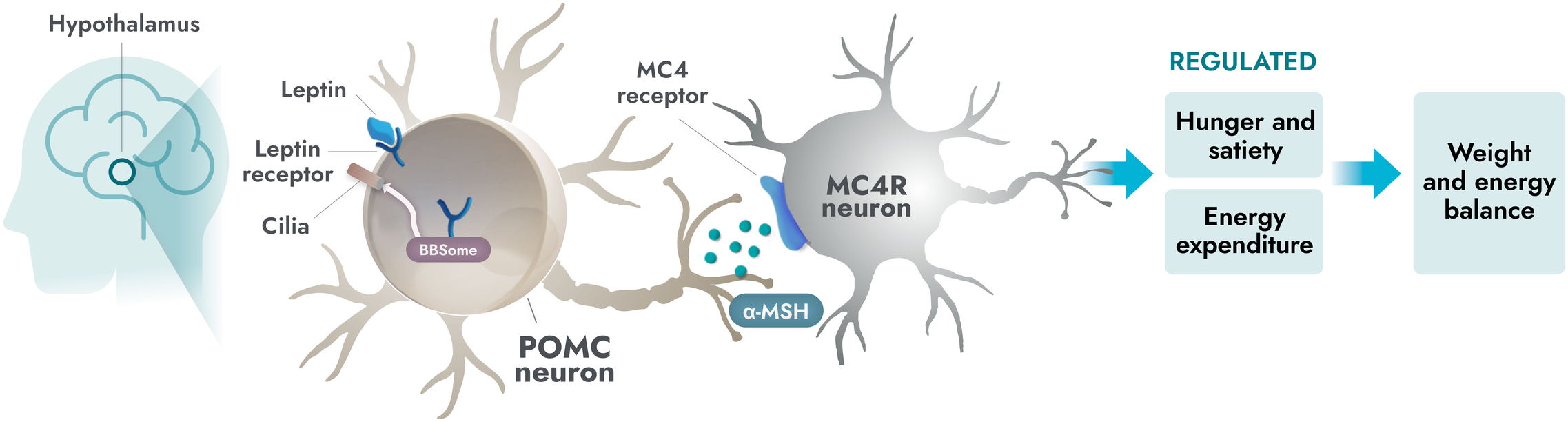

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Cilia
A structure that plays an important role in cell signaling, protein trafficking, tissue formation, cell motility, and homeostasis

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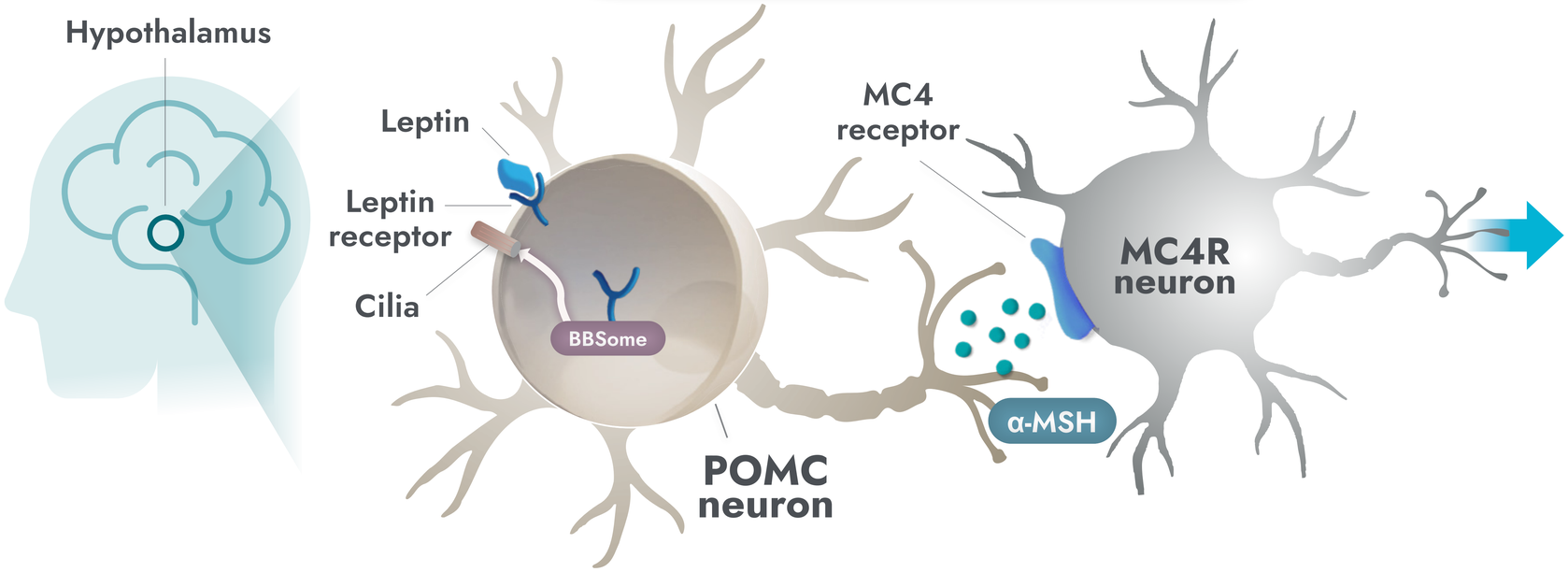

REGULATED

- Hunger and satiety
- Energy expenditure

→ Weight and energy balance

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Leptin
A satiety hormone

Impaired MC4R pathway activity[2,5,8,9]

Leptin binding to LEPR triggers a signaling cascade, including secretion of alpha-melanocyte-stimulating hormone (α-MSH) from the POMC neuron. α-MSH binds to the MC4 receptor

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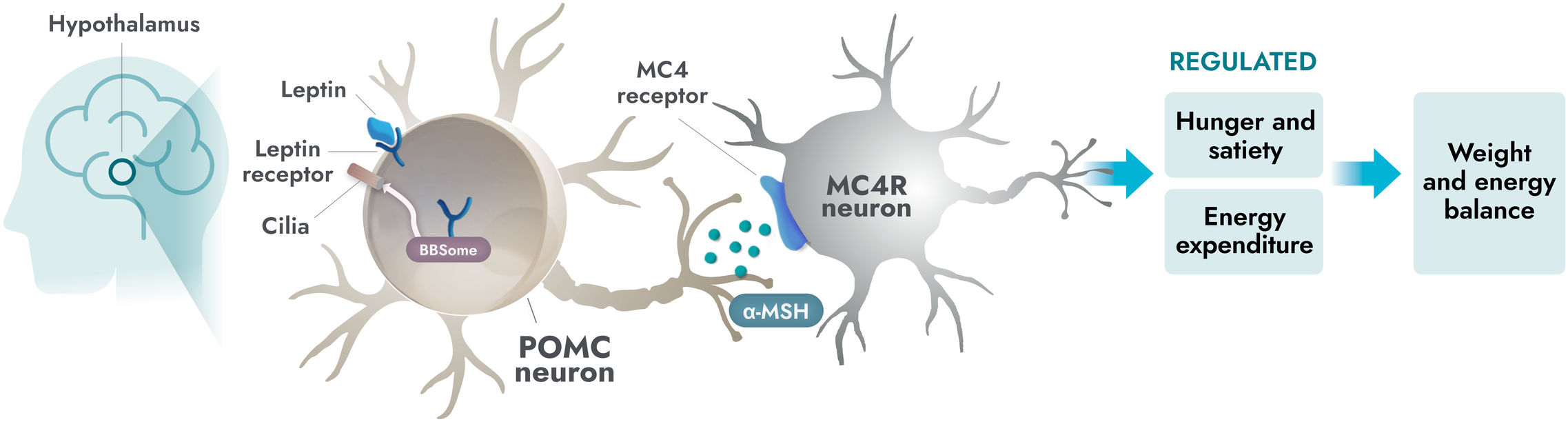

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THE MC4R PATHWAY IS A KEY SIGNALING PATHWAY IN THE HYPOTHALAMUS THAT REGULATES HUNGER AND ENERGY EXPENDITURE

Unlike general obesity, a root cause of obesity in BBS is impairment of the MC4R pathway which can occur due to ciliary dysfunction[2,8]

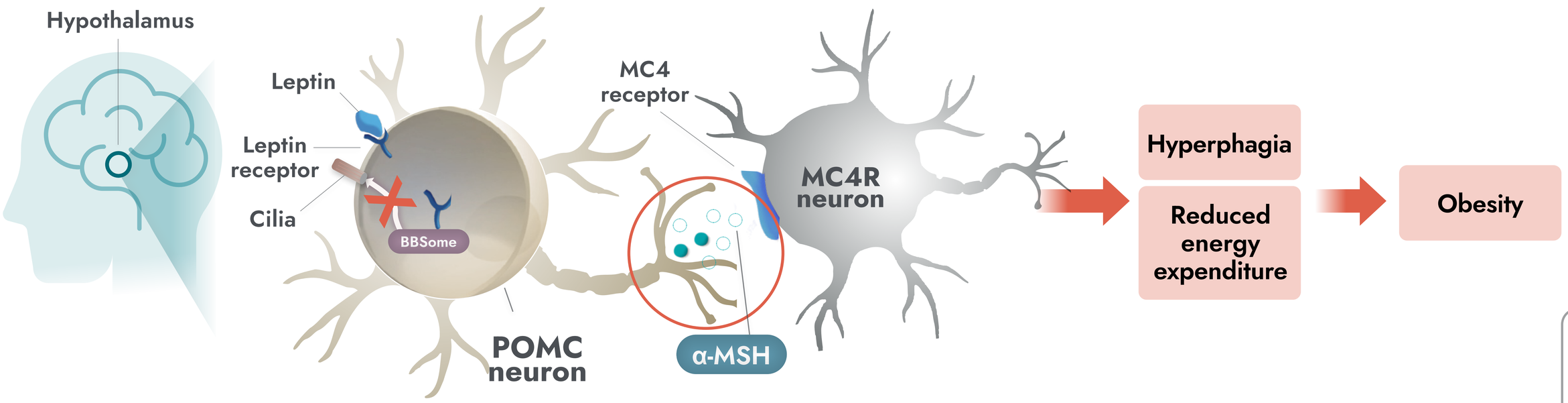
Functional MC4R pathway activity[2,5,8,9]

In people with BBS, a variant in one or more *BBS* genes can disrupt the BBSome. This causes ciliary dysfunction and disruption of LEPR signaling

Impaired MC4R pathway activity[2,5,8,9]

Alpha-melanocyte-stimulating hormone (α-MSH) production is impaired or deficient, preventing activation of the MC4 receptor

Impairment of the MC4R pathway leads to decreased satiety signaling, hyperphagia, and reduced energy expenditure. This often leads to early-onset obesity



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REFERENCES

BBS IS A RARE AUTOSOMAL RECESSIVE CILIOPATHY THAT IS CLINICALLY AND GENETICALLY DIVERSE[6,7]

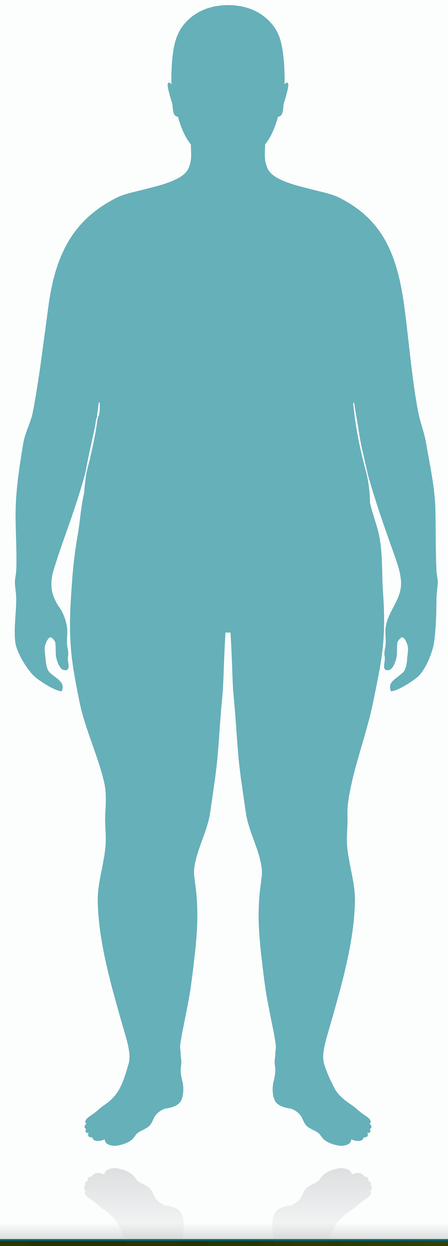
Almost all major body systems contain primary cilia, which are vital to several biological processes.[18,19]

Ciliary dysfunction impairs various systems throughout the body[18,19]

Brain[2,20,21]
- Hyperphagia
- Early-onset obesity 72–92%
- Cognitive impairment 61%

Kidneys[16,20]
- Renal anomalies 53–82%

Reproductive[22]
- Hypogonadism 59–98%



Eyes[22,23]
- Rod-cone dystrophy/ retinitis pigmentosa 93%

Skeletal[23]
- Polydactyly 63–81%

Additional clinical features of BBS may include[20,23,24]:
- **Brain:** speech delay, developmental delay, ataxia/poor coordination, anosmia/hyposmia
- **Endocrine:** diabetes mellitus
- **Heart:** congenital heart disease
- **Skeletal:** dental anomalies, brachydactyly, syndactyly

Primary cilia dysfunction within each organ system contributes to the highly variable phenotype in BBS[3,13,18]

MC4R=melanocortin-4 receptor.

REFERENCES

FACTORS CONSIDERED WHEN CLINICALLY DIAGNOSING BBS

Look at your patient's complete presentation

Clinical manifestations[4,18,23]

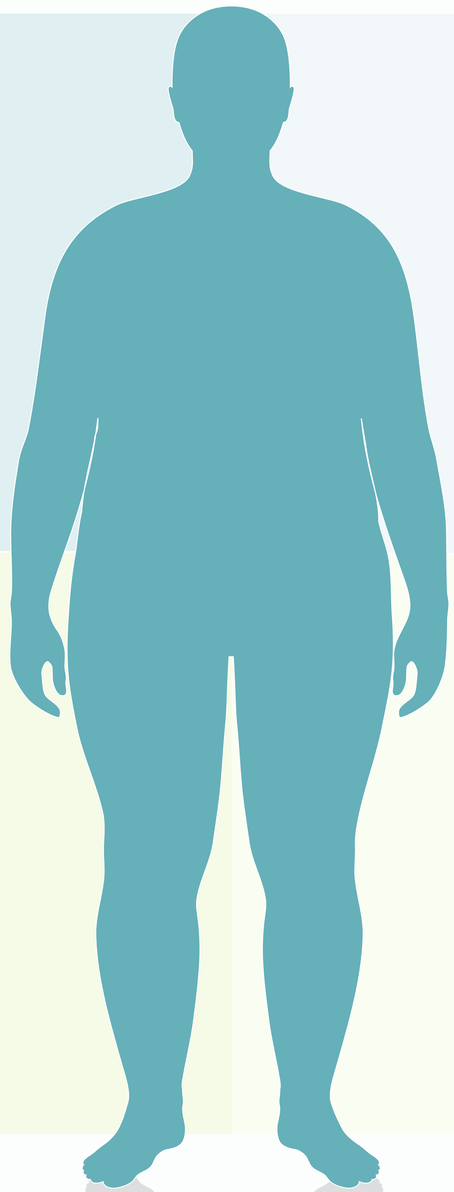
- BBS is a ciliopathy with a highly variable phenotype and clinical features that vary greatly across individuals and evolve over time
- Some features may present more mildly or slowly depending on gene variant and other factors

Clinically diagnosing BBS

Genetics[4]

- Genetic testing for BBS can provide additional diagnostic information to help inform your diagnosis. For more information, visit **UncoveringRareObesity.com**
- Results should be integrated into the overall clinical assessment of the patient and do not equate to a diagnosis on their own. Additionally, variant interpretation may change over time as the information around the genetics of BBS continues to evolve

Genetic testing



Patient history

- Review patients' complete medical history. Some clinical manifestations of BBS may have been previously treated and/or not recognized as a symptom of BBS

Key identifiable features

Recognizing BBS in Children

Recognizing BBS in Adults

Family findings[18,21]

- Family members have an increased risk of inheriting a pathogenic *BBS* gene
- Once one family member is diagnosed, others should be evaluated for BBS as well
- Phenotype can vary between family members

Dedicated ICD-10 code for BBS—Q87.83

ICD=International Classification of Diseases; MC4R=melanocortin-4 receptor.

REFERENCES

HOW BBS CAN PRESENT IN YOUR PRACTICE

Most common clinical features	Clinical manifestations		Potential assessments
Hyperphagia[2,14,17]	Chronic, pathological, insatiable hunger and impaired satiety accompanied by: • Persistent and abnormal food-seeking behaviors • Prolonged time to satiation and shortened duration of satiety	• Prolonged hunger	• Hyperphagia questionnaires • Follow up with patients/caregivers regarding behaviors around food
Obesity[2,23,26,27,40]	• Early-onset obesity, typically diffuse in children and truncal in adults • Normal birth weight, followed by rapid weight gain		• Growth chart • Track patients' BMI/BMI Z-score over time
Visual impairment[15,20,23]	• Rod-cone dystrophy/atypical retinitis pigmentosa. Symptoms include: – Night blindness – Photophobia – Loss of central and color vision – Overall loss of visual acuity – Legal blindness	• Less common features may include: – Astigmatism – Strabismus – Cataracts – Color blindness – Macular edema and degeneration	• Ophthalmologic consultation – Electroretinography test (older children and adults)
Cognitive impairment[15,20]	• Developmental delay (gross motor, fine motor, speech*/language) • Mild to moderate learning difficulties *See Speech delays and deficits on the next page	• Behavioral problems (immaturity, frustration, obsessive/compulsive nature, poor concentration/hyperactivity) • Gaze avoidance	• Developmental and/or neurocognitive assessment • Routine developmental assessments from early childhood to adulthood • Neuropsychiatric evaluation if signs/symptoms of atypical behaviors or mood disorder
Renal anomalies[15,20,23,32-34]	• Cystic tubular disease • Anatomical malformations • Urinary tract abnormalities • Hypertension • Chronic renal failure • Polyuria/polydipsia • Chronic tubulointerstitial nephritis • Glomerular defects	• Anatomical malformations at birth, including parenchymal cysts, calyceal cysts, calyceal clubbing and blunting, horseshoe kidney, fetal lobulation, scarring, unilateral renal agenesis, dysplastic kidneys, bladder obstruction, hydronephrosis, ectopic kidney, renal calculi, and vesicoureteral reflux	• Renal ultrasound • Blood pressure (24-hour monitoring if needed) • Laboratory assessments including eGFR, CBC, serum electrolytes, creatine, BUN, cystatin C • Nephrology review
Digit abnormalities[23]	• Postaxial polydactyly	• Less common features may include: – Brachydactyly – Syndactyly	• Physical examination or discussion with older patients/caregivers as extra digits are typically removed in early childhood
Genitourinary abnormalities[15,20,22] Additional clinical features ▶	**In males:** • Hypogonadism • Micropenis, small-volume testes, maldescent of testes, cryptorchidism, hypogonadotropic hypogonadism, delayed puberty, infertility	**In females:** • Uterine, fallopian, ovarian, or vaginal hypoplasia	• Laboratory tests (if indicated due to delayed puberty) – Follicle-stimulating hormone – Luteinizing hormone – Estrogen In females: • Pelvic ultrasound to assess for malformations of uterus, fallopian tubes, ovaries, and vagina

HOW BBS CAN PRESENT IN YOUR PRACTICE (cont'd)

Additional clinical features	Clinical manifestations	Potential assessments
Dental anomalies[20,33]	• Crowding • Malocclusion/micrognathia • Enamel hypoplasia • Discoloration • Microdontia • Taurodontism or short roots • Hypodontia • High-arched or deep palate • Periodontal disease	• Dental exam
Congenital heart disease[23]	Abnormalities are highly variable. Examples include: • Valvular stenosis • Patent ductus arteriosus • Cardiomyopathy	• Echocardiogram • Abdominal ultrasound to assess for laterality defects
Speech delays and deficits[20,23,28-30]	• High-pitched nasal speech/poor articulation • Unintelligible speech before age of four • Palatal incoordination • Consonant omissions/substitutions • Poor language interpretation	• Ages and Stages Questionnaires • Language Development Survey • MacArthur-Bates Communicative Development Inventories
Neurological deficits[15,20,23]	• Ataxia • Clumsiness • Poor coordination and balance • Abnormal gait	
Diabetes Mellitus[18,20]	• Non-insulin-dependent diabetes	• Fasting plasma levels of: – Glucose – Insulin • Other biochemical metrics, such as: – HbA1c – Homeostatic model assessment of insulin resistance

Most common clinical features

REFERENCES

A NO-CHARGE*, GENETIC TESTING PROGRAM FOR MC4R PATHWAY DISEASES, INCLUDING BBS

Genetic test provides insights

The gene panel includes 87 genes (29 genes associated with BBS) and 1 chromosome region, reflective of nearly all of the most frequently tested genes associated with obesity. This is not a test for Prader-Willi syndrome.[35,36]

Tailored support for results interpretation

The program provides you with access to a geneticist to help interpret results, as well as board-certified genetic counselors for your patients. Services are provided through third-party partners.

Testing conducted by laboratory partner

DNA testing is conducted by PreventionGenetics, a CLIA-accredited clinical laboratory.

Blood and OCD-100 buccal swab sample collection kits are available.

Go deeper into the role of genetic testing for diagnosis ▶

For more information about the genetic testing program, visit UncoveringRareObesity.com

*Rhythm Pharmaceuticals covers the cost of the test and provides sample collection kits. Patients are responsible for office visit, sample collection, and other costs.

CLIA=Clinical Laboratory Improvement Amendments; MC4R=melanocortin-4 receptor.

ICD=International Classification of Diseases; MC4R=melanocortin-4 receptor.

BBS IS CLINICALLY AND GENETICALLY DIVERSE, SO NOT ALL PEOPLE WITH BBS WILL PRESENT THE SAME WAY OR WITH ALL THESE MOST COMMON FEATURES[18]

	Birth	First years of life (0 to 5 years)	Early childhood (up to 10 years)	Adolescence to adulthood (>10 years)
Polydactyly[23]	Extra digits (postaxial)	Typically surgically removed		
Renal anomalies[32]	Anatomical malformations	Progressive kidney disease	Polyuria/Polydipsia	Chronic kidney disease
Hyperphagia and early-onset obesity[17,23,40,41]	Normal birth weight	Rapid weight gain leading to early-onset, severe obesity; unusual food seeking	Hyperphagia and severe obesity persist	Continued hyperphagia and severe obesity, presenting as truncal obesity for adults
Cognitive impairment[20,23]		Developmental delay, speech delay	Specialized schooling needs, behavioral difficulties	Learning difficulties
Visual impairment[23,42]			Progressive vision loss, night blindness	Legal blindness
Hypogonadism[20,23]				Delayed puberty, genital anomalies

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REFERENCES

SEVERAL FACTORS ARE CONSIDERED WHEN DIAGNOSING BBS

Look at your patient's complete presentation

Clinical manifestations[6,7,15]

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Recognizing BBS in Children

Recognizing BBS in Adults

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Dedicated ICD-10 code for BBS—**Q87.83**

ICD=International Classification of Diseases; MC4R=melanocortin-4 receptor.

REFERENCES

RECOGNIZING BBS IN CHILDREN[43]

- Due to the progressive onset of clinical symptoms, patients may not meet the diagnostic criteria early in life, leading to a potential delay in diagnosis
- Therefore, genetic testing may play a critical diagnostic role in young children

Diagnosing patients as early as possible is key to reducing their weight gain trajectory and managing associated obesity outcomes. It may also help reduce the burden of hyperphagia.

SEVERAL FACTORS ARE CONSIDERED WHEN DIAGNOSING BBS

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Clinical manifestations[6,7,15]

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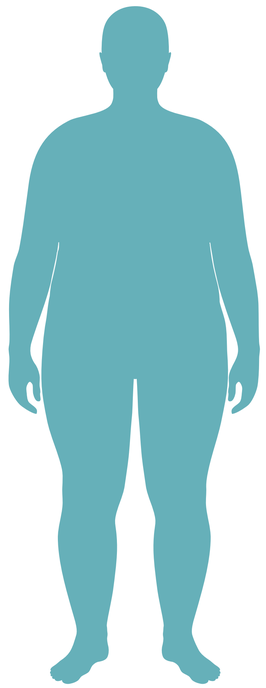


RECOGNIZING BBS IN ADULTS[20,44]

Many people with BBS over 30 may not have been diagnosed as children due to the following limitations:

- Clinical diagnosis: Clinical diagnosis criteria were newly defined when they were children. Clinical recognition of the syndrome also remains low due to variability in phenotypical presentation.
- Genetic confirmation: In 1999, only 4 of the current *BBS* genes had been identified. Also, there has been historically low genetic-testing utilization due to a lack of availability, insurance coverage, and treatment for BBS.

It is important to recognize the symptoms of BBS in adults to ensure they are diagnosed appropriately.

REFERENCES

BBS CAN CAUSE A SIGNIFICANT PATIENT BURDEN

Negative impact on quality of life[15,18]

People with BBS and their caregivers report substantial burden, including a negative impact on their emotional well-being, mental health, social life, and family relations.

Hyperphagia is considered one of the most distressing symptoms for people with BBS and their caregivers, with both reporting a moderate or significant impact on daily life. Patients reported impacts on:

- **Leisure: 62%**
- **Concentrating in school: 57%**
- **Mood/emotion: 56%**
- **Sleep: 54%**
- **Familial relationships: 51%**

High risk of long-term complications[3,18,40]

The prevalence of obesity increases year over year in people with BBS. Nearly 93% are categorized as having overweight or obesity by early childhood.

Obesity in people with BBS can exacerbate long-term, serious comorbidities that may include:

- **Diabetes**
- **Cardiovascular disease**
- **Kidney failure**
- **Hypertension**
- **Non-alcoholic fatty liver disease**
- **Overall clinical and mental health**

Renal anomalies due to BBS can be impacted by early-onset obesity, further compounding renal impairment.

It is important to identify hyperphagia and early-onset obesity given the risk of potential long-term complications[3,18,40]

REFERENCES

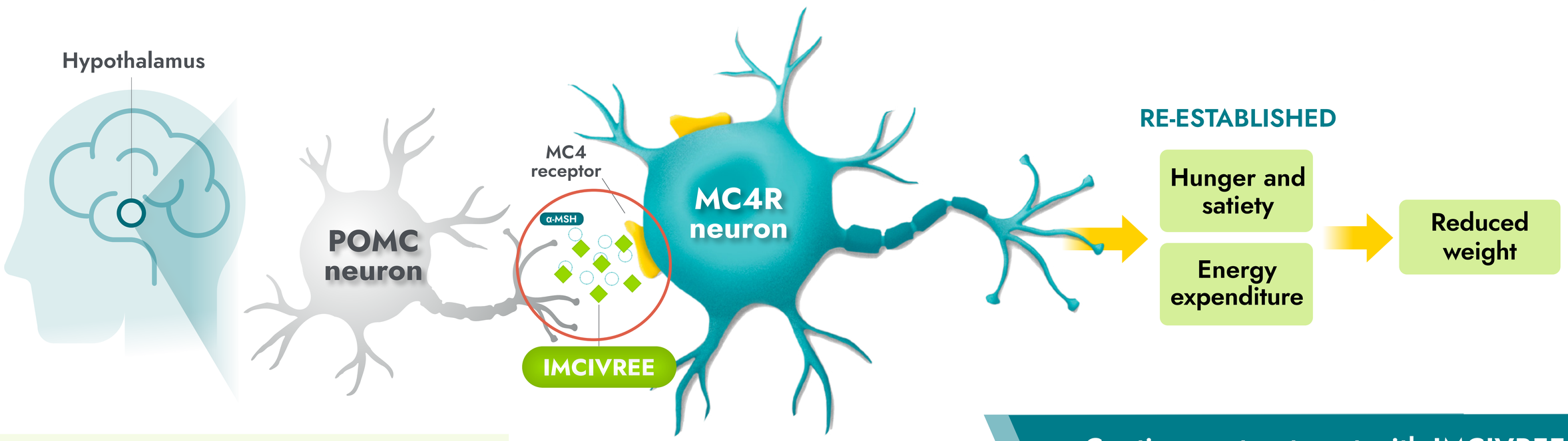
IMCIVREE IS THE FIRST AND ONLY PRECISION MEDICINE TO TARGET IMPAIRMENT OF THE HYPOTHALAMIC MC4R PATHWAY, A ROOT CAUSE OF HYPERPHAGIA AND OBESITY IN BBS

Re-established MC4R pathway activity[1,45,46]

IMCIVREE, an MC4R agonist, targets a root cause of obesity due to BBS

IMCIVREE acts in place of alpha-melanocyte-stimulating hormone (α-MSH) to activate the MC4 receptor and help re-establish MC4R pathway activity

Re-established pathway activity helps to bring hunger and satiety signals, and energy expenditure, into balance. This can lead to reduced weight



IMCIVREE is foundational to the long-term treatment of obesity due to BBS

Continuous treatment with IMCIVREE helps re-establish and maintain MC4R pathway activity[1,47]

MC4R=melanocortin-4 receptor; POMC=proopiomelanocortin.

Important Safety Information

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

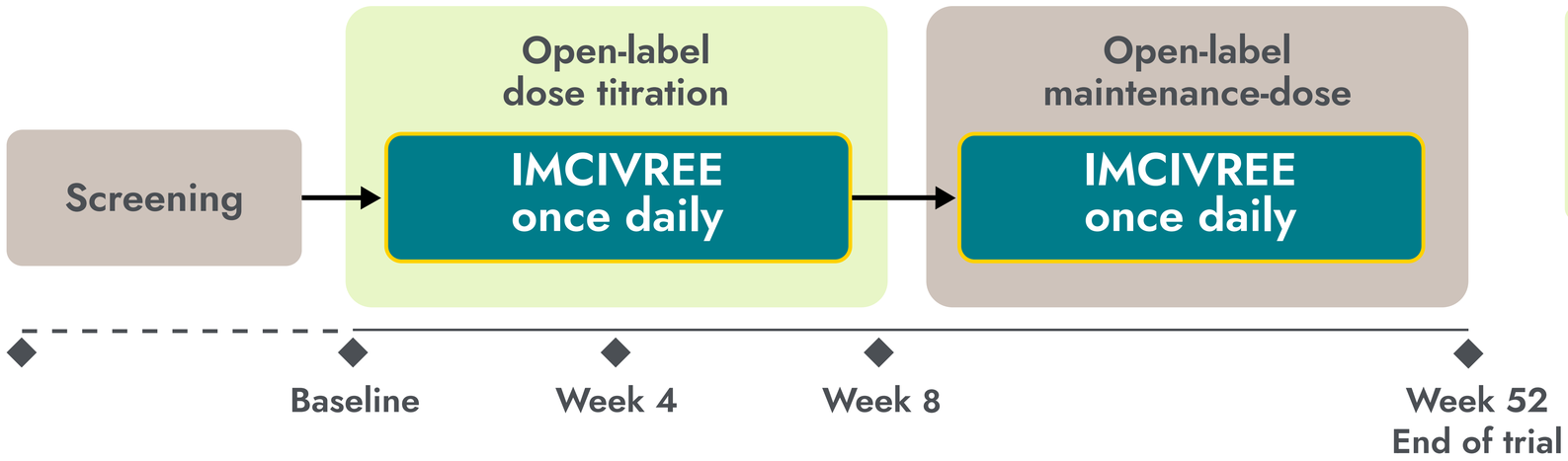
Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

ONLY IMCIVREE WAS STUDIED ACROSS TWO, FIRST-EVER PHASE 3 CLINICAL TRIALS DEDICATED TO OBESITY AND HUNGER REDUCTION IN PEOPLE WITH BBS[1,46-48]

The efficacy and safety of IMCIVREE for the reduction of weight were studied in the first-ever Phase 3 clinical trial for children 2 to <6 years of age with obesity due to BBS[1,48]*



Initial dose of 0.5 mg QD was increased by 0.5 mg every 2 weeks if tolerated to baseline body weight

Weight, kg	15 to <20	20 to <30	30 to <40	≥40
Dose, mg	0.5	1.0	1.5	2.0

*7 patients with POMC or LEPR deficiency and 5 patients with BBS participated in the trial.

Study design: The study enrolled patients 2 to <6 years of age with obesity and hunger due to genetically confirmed BBS. Enrolled patients had a baseline BMI ≥97th percentile using growth chart assessments. IMCIVREE dose titration occurred over an 8-week period, followed by a 44-week, open-label treatment period with IMCIVREE. Efficacy and safety analysis were conducted at the end of treatment in 12 patients (7 with POMC or LEPR deficiency and 5 with BBS). Study assessments were performed approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52. Given the rarity of BBS and the pediatric age group being studied, as well as the absence of effective treatment for this condition, no placebo or active control group was used.

+ Study endpoints

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

ONLY IMCIVREE WAS STUDIED ACROSS TWO, FIRST-EVER PHASE 3 CLINICAL TRIALS DEDICATED TO OBESITY AND HUNGER REDUCTION IN PEOPLE WITH BBS[1,46-48]

STUDY DESIGN: YOUNG CHILDREN (2 TO <6) | STUDY DESIGN: CHILDREN + ADULTS (6+) | OVERALL BMI REDUCTION

The efficacy and safety of IMCIVREE for the reduction of weight were studied in the first-ever Phase 3 clinical trial for children 2 to <6 years of age with obesity due to BBS[1,48]*

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*7 patients with P

Study design
≥97th percent
with IMCIVREE. Efficacy and safety analysis were conducted at the end of treatment in 12 patients (7 with POMC or LEPR deficiency and 5 with BBS). Study assessments were performed approximately every 4 weeks through Week 20 and then approximately every 8 weeks through Week 52. Given the rarity of BBS and the pediatric age group being studied, as well as the absence of effective treatment for this condition, no placebo or active control group was used.

STUDY ENDPOINTS[48]

- **Primary Endpoint:** The mean percent change in BMI from baseline to Week 52
- The proportion of patients demonstrating a response to IMCIVREE (defined as a decrease from baseline to Week 52 in BMI Z-score of ≥0.2)
- The mean change in BMI Z-score
- The mean change in percent of the 95th percentile of BMI
- Hunger
- Waist circumference
- Caregiver burden

Study endpoints

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

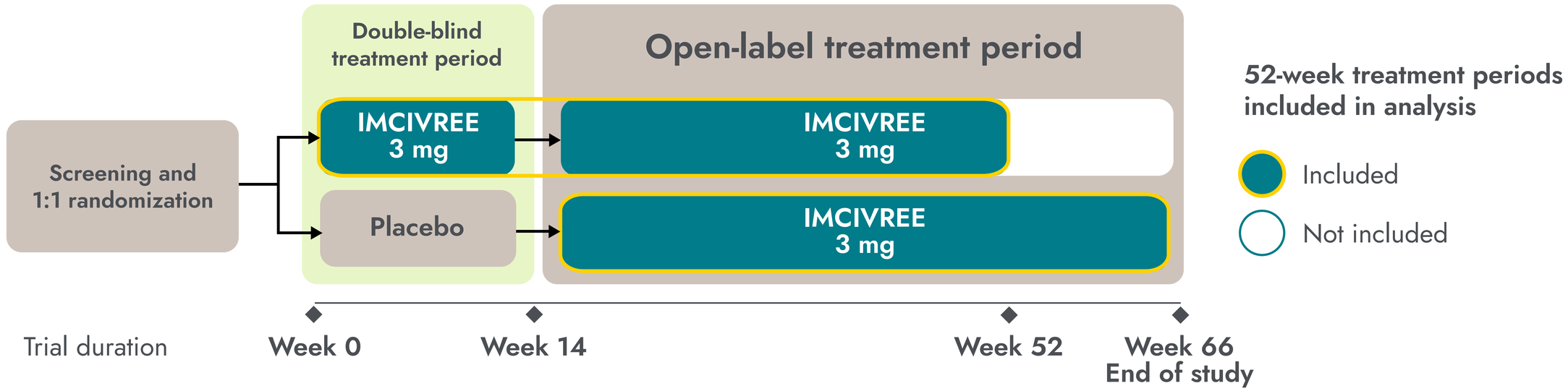
Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

ONLY IMCIVREE WAS STUDIED ACROSS TWO, FIRST-EVER PHASE 3 CLINICAL TRIALS DEDICATED TO OBESITY AND HUNGER REDUCTION IN PEOPLE WITH BBS

The efficacy and safety of IMCIVREE for the reduction of weight and hunger in people 6 years of age and older with BBS were studied in a Phase 3 trial with a randomized, double-blind, placebo-controlled period



50% of enrolled patients were children or adolescents who would normally be expected to gain weight as they grow[1,49]

Study design: The study enrolled patients ≥6 years of age with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of ≥30 kg/m^2 and pediatric patients had weight in the ≥97th percentile using growth chart assessments. To maintain the blind during period 1 (14-week placebo-controlled period), dose titration to a fixed dose of 3 mg given subcutaneously once daily was performed during the first 2 weeks of both period 1 and period 2 (52-week open-label period). Efficacy analyses were conducted in 44 patients at the end of period 1 (week 14, placebo-controlled data) and in 31 patients during the active-treatment period, defined as the period from randomization to week 52 in patients initially randomized to IMCIVREE, and from week 14 to week 66 in patients initially randomized to placebo. Analyses of the active-treatment period include patients who had either completed 52 weeks from the start of IMCIVREE treatment or discontinued the study early at the time of the prespecified data cutoff.[1]

+ Study endpoints

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

ONLY IMCIVREE WAS STUDIED ACROSS TWO, FIRST-EVER PHASE 3 CLINICAL TRIALS DEDICATED TO OBESITY AND HUNGER REDUCTION IN PEOPLE WITH BBS

The efficacy and safety of IMCIVREE for the reduction of weight and hunger in people 6 years of age and older with BBS were studied in a Phase 3 trial with a randomized, double-blind, placebo-controlled period

STUDY ENDPOINTS[1,47]

- **Primary Endpoint of Interest:** The mean percent change in BMI from baseline to Week 52
- Proportion of patients who demonstrated a response to IMCIVREE after Week 52
- The proportion of patients demonstrating a mean percent change in hunger scores at Week 52
- The proportion of patients who achieve a ≥25% improvement in the weekly average of the daily hunger score
- Blood pressure*
- Lipids*
- Waist circumference*

*Because of the limited number of patients studied and the lack of control group, the treatment effects on these parameters could not be accurately quantified.

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Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE®
(setmelanotide) injection

REFERENCES

ONLY IMCIVREE WAS STUDIED ACROSS TWO, FIRST-EVER PHASE 3 CLINICAL TRIALS DEDICATED TO OBESITY AND HUNGER REDUCTION IN PEOPLE WITH BBS

IMCIVREE DELIVERED BMI REDUCTIONS

~10% mean BMI reduction after 1 year in young children aged 2 to <6 years[1]

~8% mean BMI reduction after 1 year in children and adults aged ≥6 years[1]

Patients were not required to change their diet or exercise routine[50]

Supportive of the effect of IMCIVREE on weight loss, there were general numeric improvements in blood pressure, lipids, and waist circumference. However, because of the limited number of patients studied and the lack of a control group, the treatment effects on these parameters could not be accurately quantified.[1,48]

IMCIVREE is foundational to the long-term treatment of obesity due to BBS as the only precision medicine designed to re-establish MC4R pathway activity. This pathway activity is critical to maintain regulated satiety signaling, energy expenditure, and weight.[1]

Actor portrayals.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

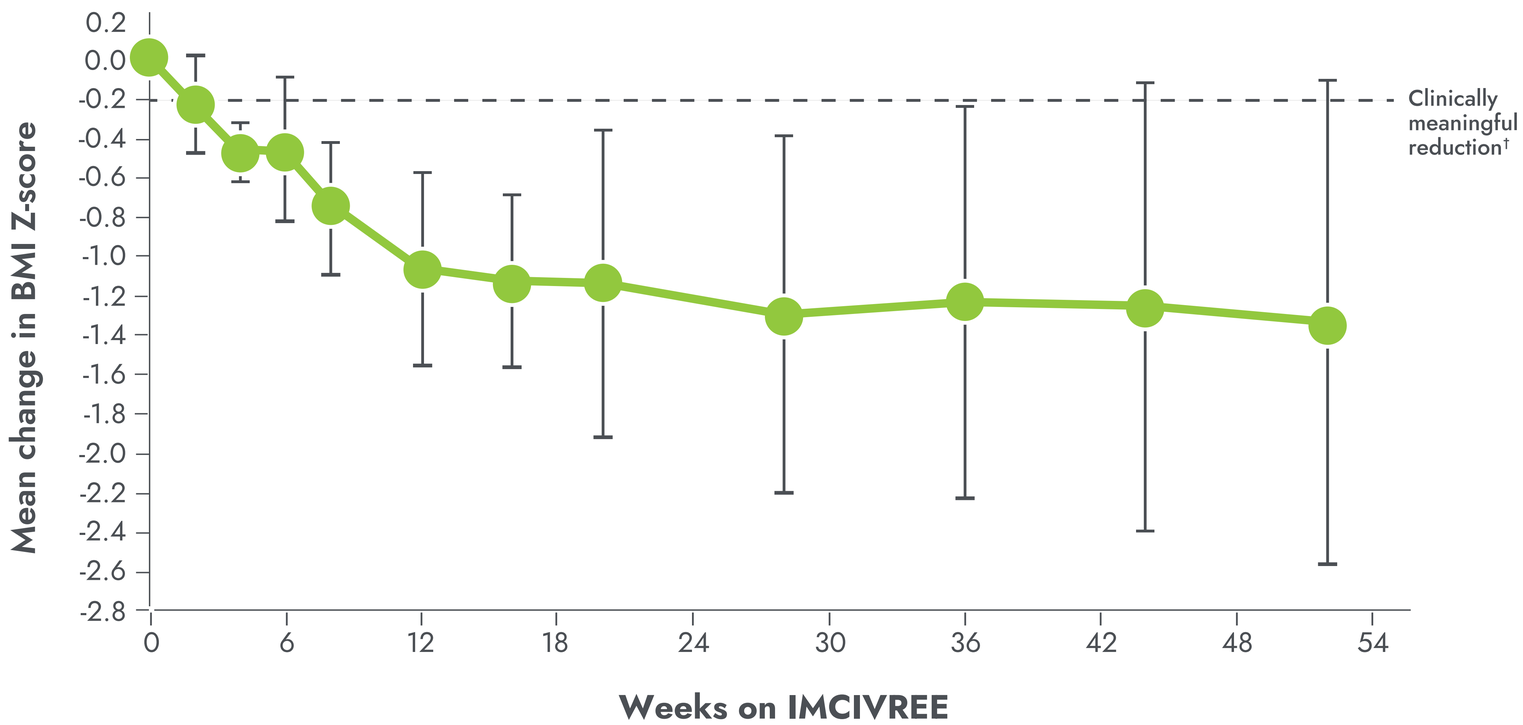
REFERENCES

In patients 2 to <6 years of age with BBS

IMCIVREE DELIVERED EARLY AND CLINICALLY MEANINGFUL WEIGHT REDUCTION[1,48]

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | CHANGE IN BMI PERCENTILE

BMI Z-SCORE REDUCTION IN PATIENTS 2 TO <6 YEARS OF AGE[51]*



Clinically meaningful -1.3 mean change in BMI Z-score at week 52[48]

- A BMI Z-score is a reliable measure of weight in children who are still growing because it accounts for height, age, and gender[26]

*Data shown include only patients who received 52 weeks of IMCIVREE at the time of the analysis (n=5).[48]
†A clinically meaningful reduction is generally considered a ≥0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.[48]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

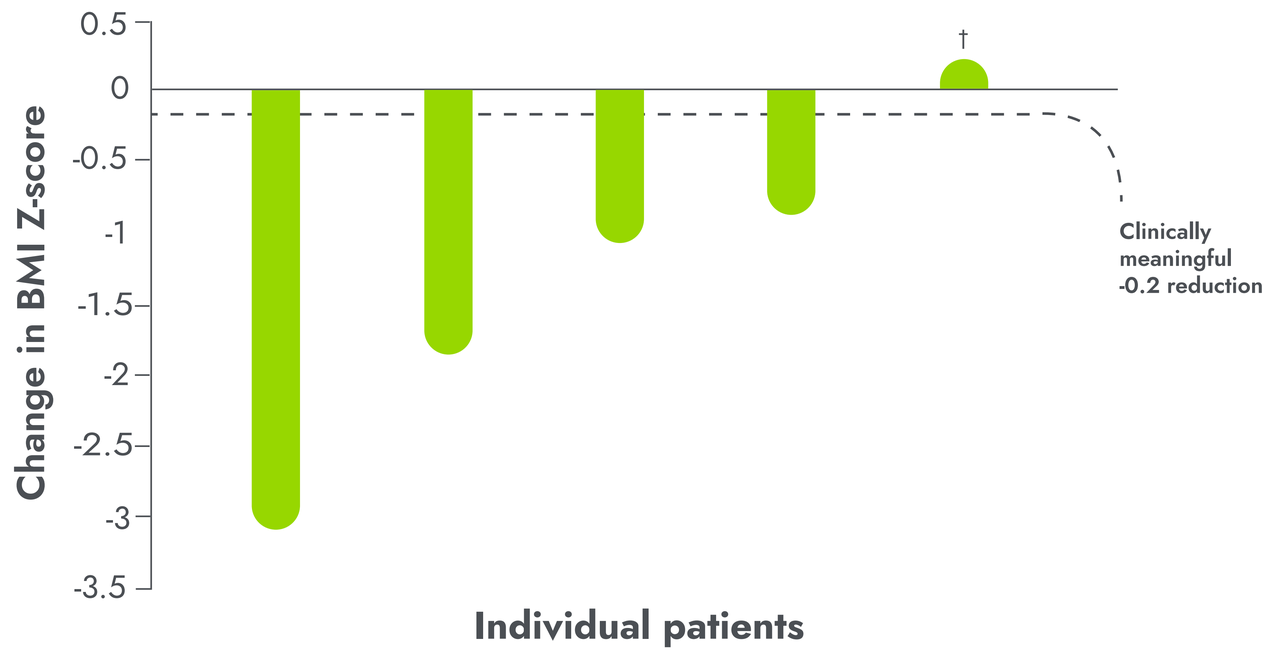
REFERENCES

In patients 2 to <6 years of age with BBS

IMCIVREE DELIVERED EARLY AND CLINICALLY MEANINGFUL WEIGHT REDUCTION[1,48]

BMI Z-SCORE REDUCTION | **INDIVIDUAL RESULTS** | CHANGE IN BMI PERCENTILE

CHANGE IN BMI Z-SCORE* FROM BASELINE IN PATIENTS 2 TO <6 YEARS OF AGE AFTER 52 WEEKS (n=5)[48]



80% of patients achieved a clinically meaningful reduction of ≥0.2 in BMI Z-score[48]

*BMI Z-score was used to measure the reduction in BMI in children. A clinically meaningful reduction is generally considered to be a ≥0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.[48]

†Patient was not compliant with dosing[48]

Patients were not required to change their diet or exercise routine[50]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

Please see additional Important Safety Information and full Prescribing Information.

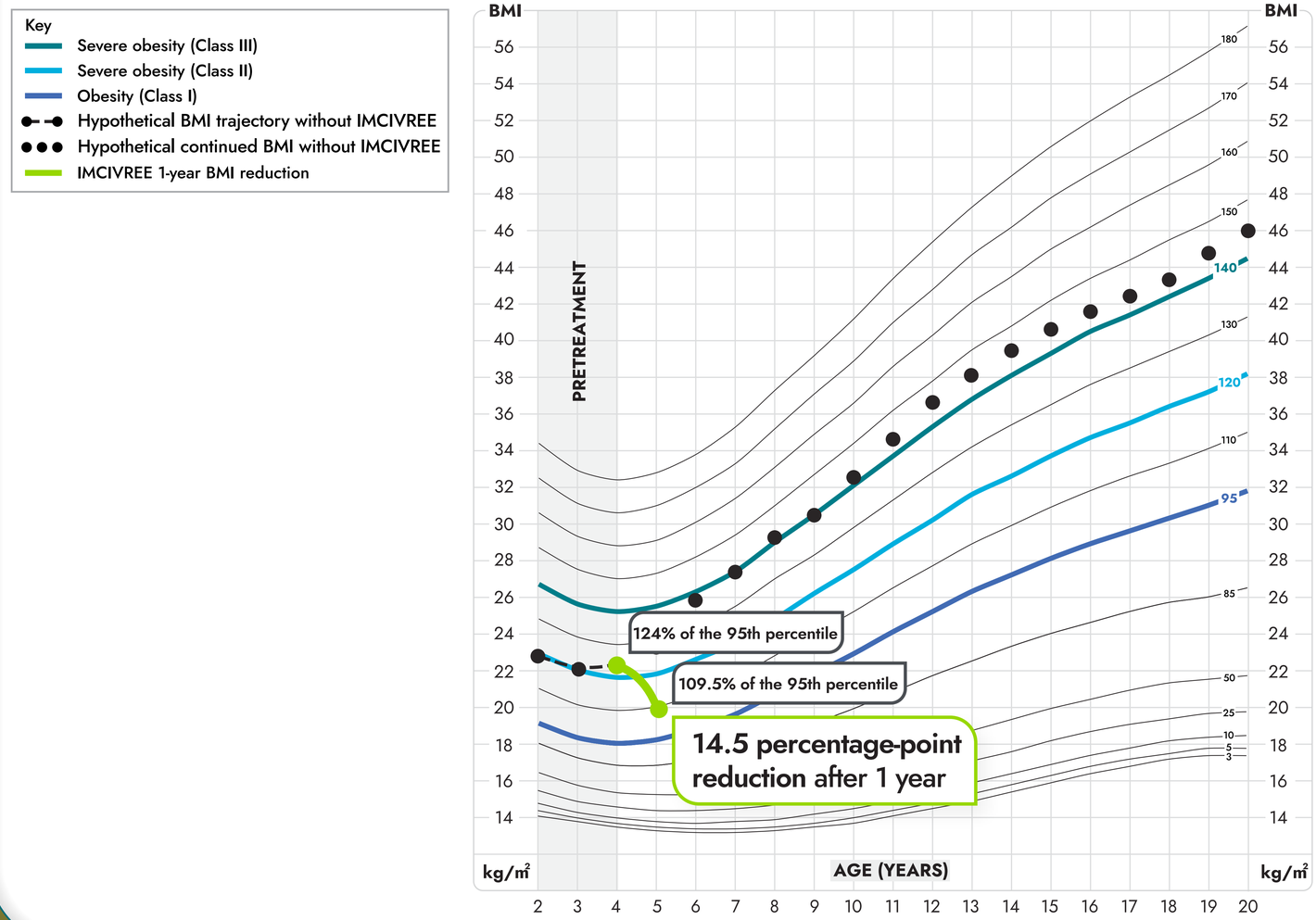
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients 2 to <6 years of age with BBS

IMCIVREE DELIVERED EARLY AND CLINICALLY MEANINGFUL WEIGHT REDUCTION

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | **CHANGE IN BMI PERCENTILE**



IMCIVREE REDUCED THE SEVERITY OF OBESITY DUE TO BBS[48]

This chart is a visual representation of what a hypothetical child with BBS who started IMCIVREE at age 4* may experience in BMI reduction after 1 year based on data from the Phase 3 trial

- **Treating early with IMCIVREE can lead to a healthier weight-gain trajectory[1,48]**

*Growth chart is based on females 2 to 20 years of age and is for illustrative purposes only.

Figure modeled after Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. *Pediatrics*. 2012;130(6):1136-1140.

Important Safety Information (cont'd)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

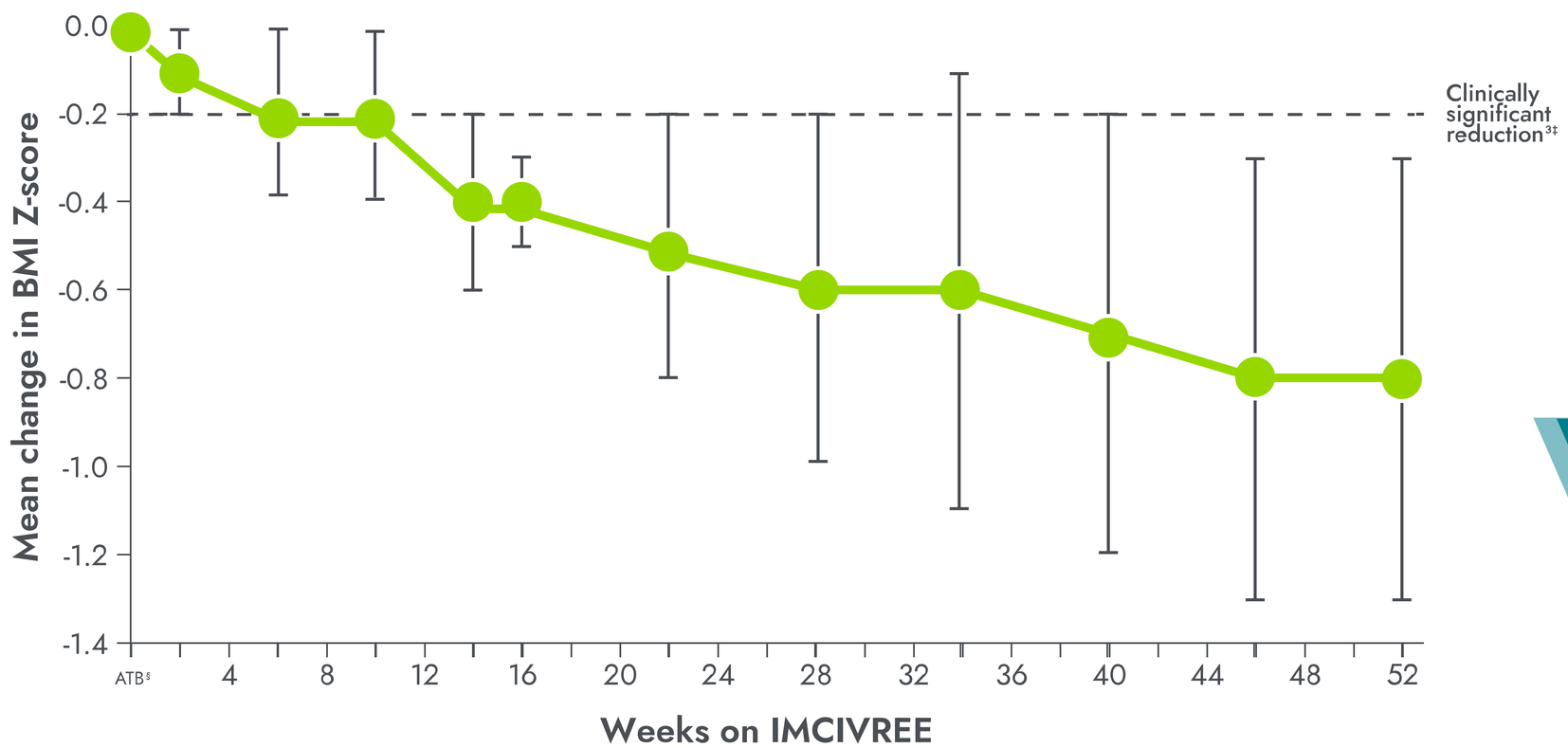
REFERENCES

In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[47,50,53]

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | CHANGE IN BMI PERCENTILE | HUNGER REDUCTION

BMI Z-SCORE* REDUCTION IN PATIENTS 6 TO <18 YEARS OF AGE†



- 14-week weight reduction results vs placebo
- 24-month long-term extension trial

Clinically significant -0.8 mean change in BMI Z-score at week 52[47,53]

- **Sustained mean reductions in BMI Z-score at 24 months in a long-term extension study[54]**

*BMI Z-score was an exploratory endpoint used to measure the reduction in BMI in children. A BMI Z-score is a reliable measure of weight in children who are still growing because it accounts for height, age, and gender.[47]
†Data shown includes only patients who received 52 weeks of IMCIVREE at the time of the analysis. Population sizes ranged from 8 to 16, with n=14 at 52 weeks on active treatment. Error bars are the standard deviation.[47]
‡A clinically significant reduction is generally considered a ≥0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.[53]
§ATB=active treatment baseline, defined as the last measurement before the first dose of IMCIVREE; ie, week 0 for IMCIVREE group and week 14 for placebo group.[47]

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

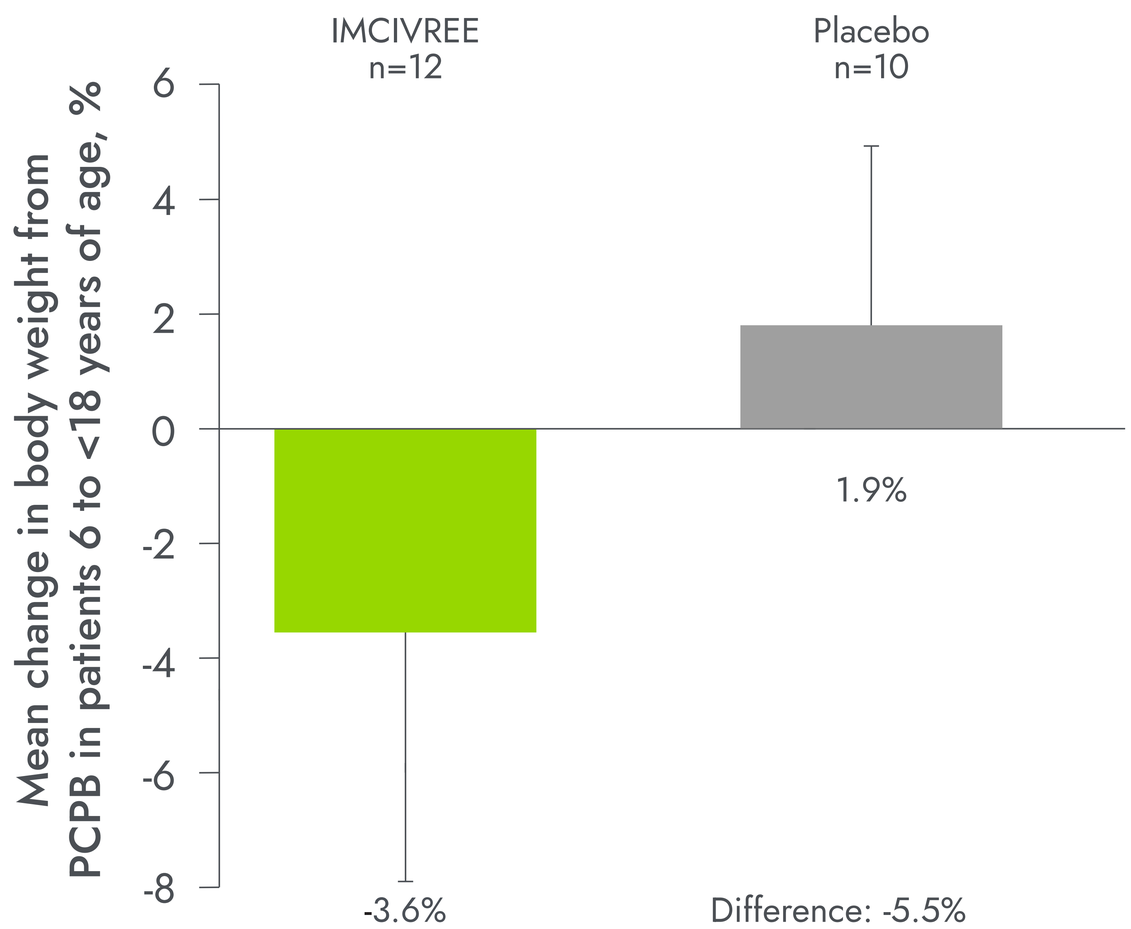
In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION

In patients 6 to <18 years of age with BBS

IMCIVREE SIGNIFICANTLY REDUCED WEIGHT[47]

WEIGHT CHANGES IN PIVOTAL AND SUPPLEMENTAL PATIENTS 6 TO <18 YEARS OF AGE WITH BBS DURING THE 14-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED PERIOD[47]*



*Results in sub-population based on post hoc analysis. Supplemental patients were enrolled after the pivotal cohort had begun treatment. None of the supplemental patients had completed 52 weeks of IMCIVREE treatment at the time of data analysis.[47]

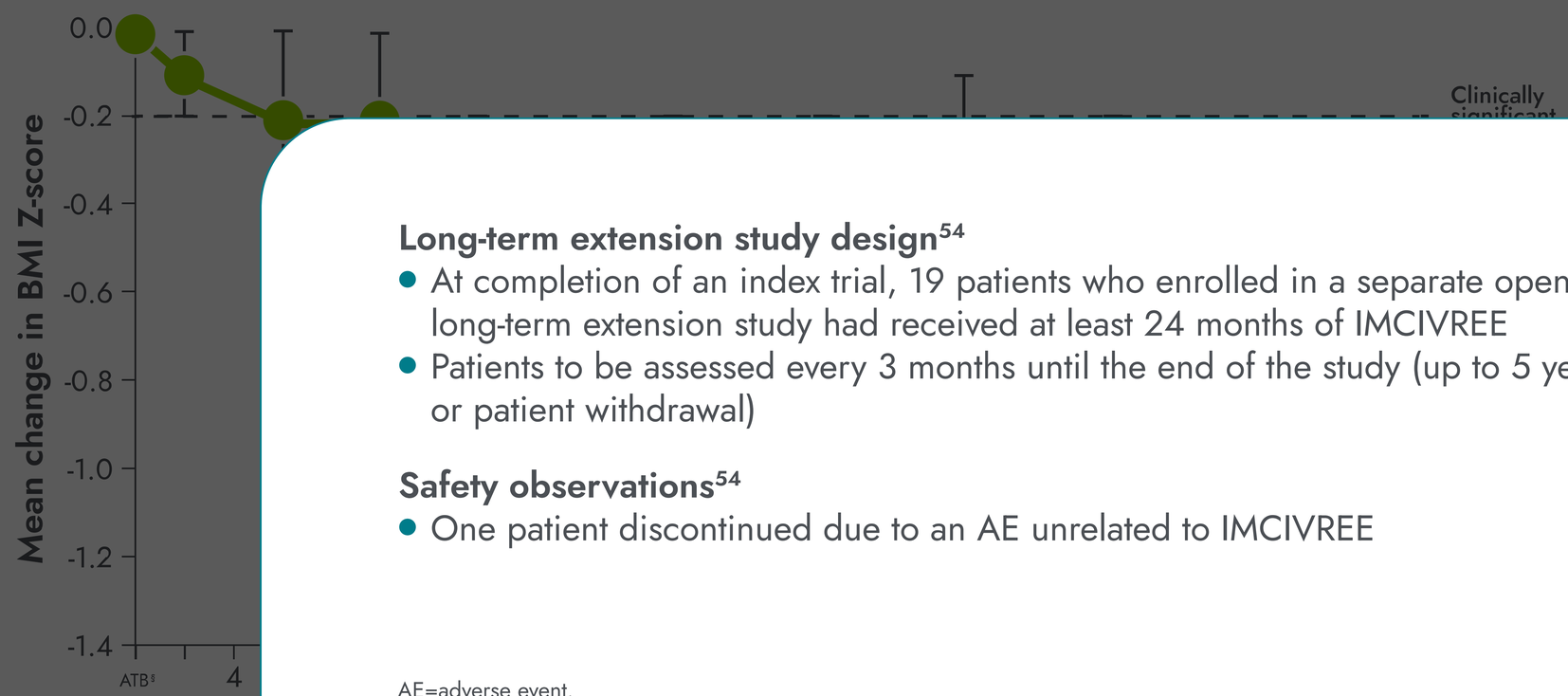
PCPB=placebo-controlled period baseline.

In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | CHANGE IN BMI PERCENTILE | HUNGER REDUCTION

BMI Z-SCORE* REDUCTION IN PATIENTS 6 TO <18 YEARS OF AGE†



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Long-term extension study design[54]

- At completion of an index trial, 19 patients who enrolled in a separate open-label, long-term extension study had received at least 24 months of IMCIVREE
- Patients to be assessed every 3 months until the end of the study (up to 5 years or patient withdrawal)

Safety observations[54]

- One patient discontinued due to an AE unrelated to IMCIVREE

AE=adverse event.

*BMI Z-score was an exploratory endpoint used to measure the reduction in BMI in children. A BMI Z-score is a reliable measure of weight in children who are still growing because it accounts for height, age, and gender.
†Data shown includes only patients who received 52 weeks of IMCIVREE at the time of the analysis. Population sizes ranged from 8 to 16, with n=14 at 52 weeks on active treatment. Error bars are the standard deviation.
‡A clinically significant reduction is generally considered a ≥0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.
§ATB=active treatment baseline, defined as the last measurement before the first dose of IMCIVREE; ie, week 0 for IMCIVREE group and week 14 for placebo group.

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

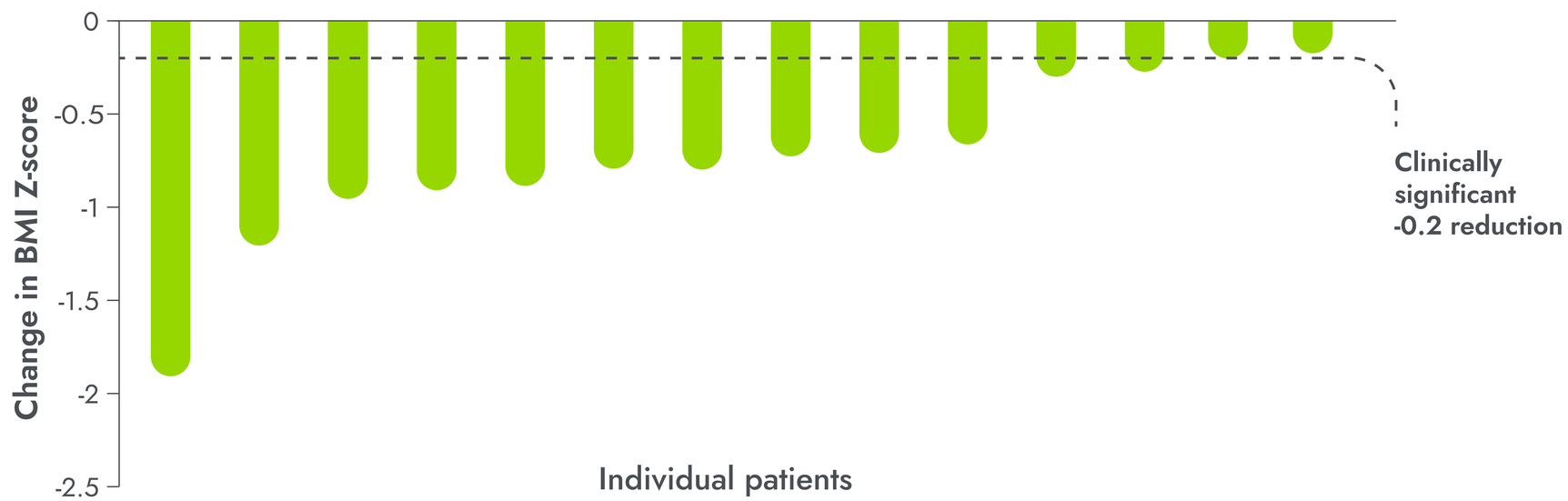
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION [47,50,53]

CHANGE IN BMI Z-SCORE FROM BASELINE IN PATIENTS 6 TO <18 YEARS OF AGE AFTER 52 WEEKS (n=14)[50]



86% of patients achieved a clinically significant ≥0.2 mean reduction* in BMI Z-score[47,53]

— 100% of patients 6 to <12 years of age achieved a clinically significant ≥0.2 mean reduction in BMI Z-score (n=3)[50,53]

+ 24-month long-term extension trial results

Patients were not required to change their diet or exercise routine[50]

*BMI Z-score was an exploratory endpoint used to measure the reduction in BMI in children. A clinically significant reduction is generally considered to be a ≥0.2 reduction in BMI Z-score. A 0.2 reduction is comparable to weight loss of approximately 5%.[53]

Important Safety Information (cont'd)

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

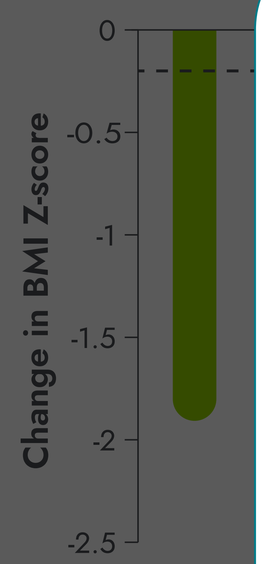
REFERENCES

In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[44,45,48]

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | CHANGE IN BMI PERCENTILE | HUNGER REDUCTION

CHANGE IN BMI Z-SCORE FROM BASELINE IN PATIENTS



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IMCIVREE DELIVERED SUSTAINED WEIGHT REDUCTION[54,*]

24-month BMI Z-score results from a long-term extension study in patients 6 to <18 years of age with BBS (n=12):

- One patient discontinued due to an AE unrelated to IMCIVREE[54]

Long-term extension study design[50,54]

- At completion of an index trial, 19 patients who enrolled in a separate open-label, long-term extension study had received at least 24 months of IMCIVREE
- Patients to be assessed every 3 months until the end of the study (up to 5 years or patient withdrawal)

*Compared with measures at index trial baseline.[47]

AE=adverse event.

Important Safety Information (cont'd)

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

Please see additional Important Safety Information and full Prescribing Information.

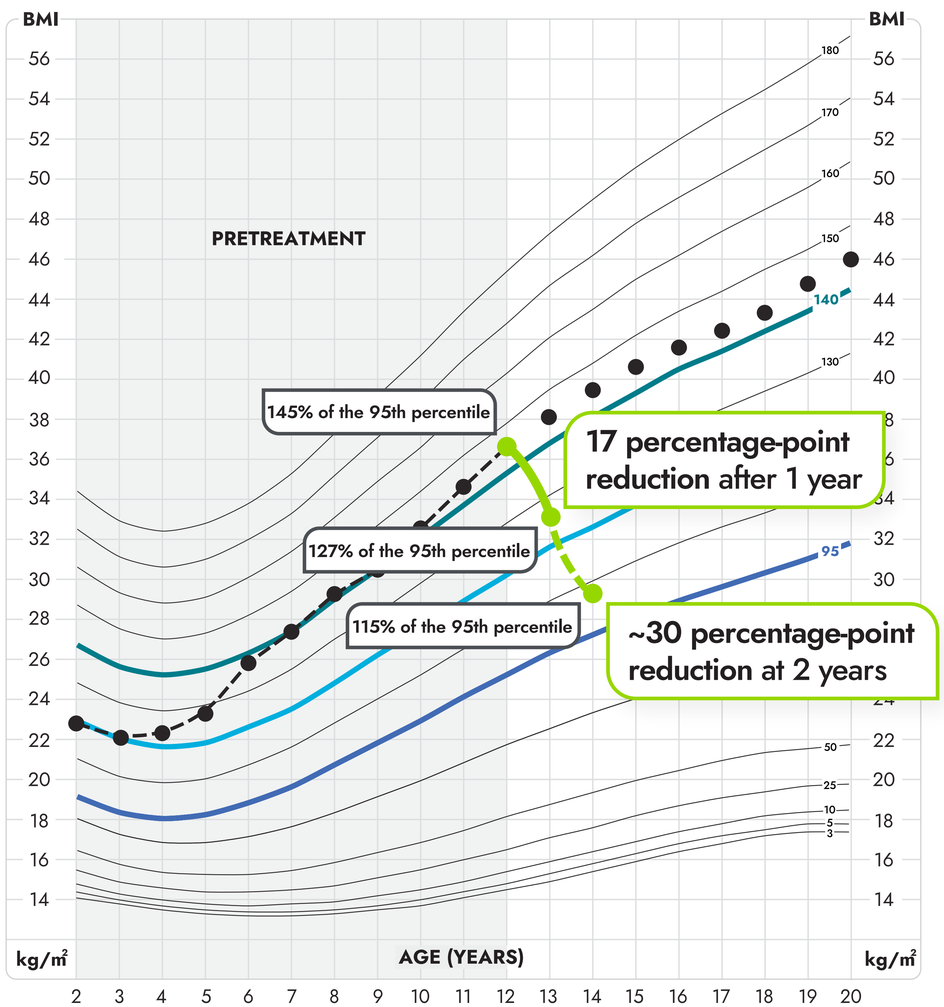
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients 6 to <18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION

BMI Z-SCORE REDUCTION | INDIVIDUAL RESULTS | **CHANGE IN BMI PERCENTILE** | HUNGER REDUCTION



IMCIVREE SIGNIFICANTLY REDUCED THE SEVERITY OF OBESITY DUE TO BBS[47,53-55]

This chart is a visual representation of what a hypothetical child with BBS who started IMCIVREE at age 12* may experience in BMI reduction after 1 year and 2 years, based on data from the Phase 3 trial and a separate long-term extension trial

*Growth chart is based on females 2 to 20 years of age and is for illustrative purposes only.

Figure modeled after Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. *Pediatrics*. 2012;130(6):1136-1140.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Please see additional Important Safety Information and full Prescribing Information.

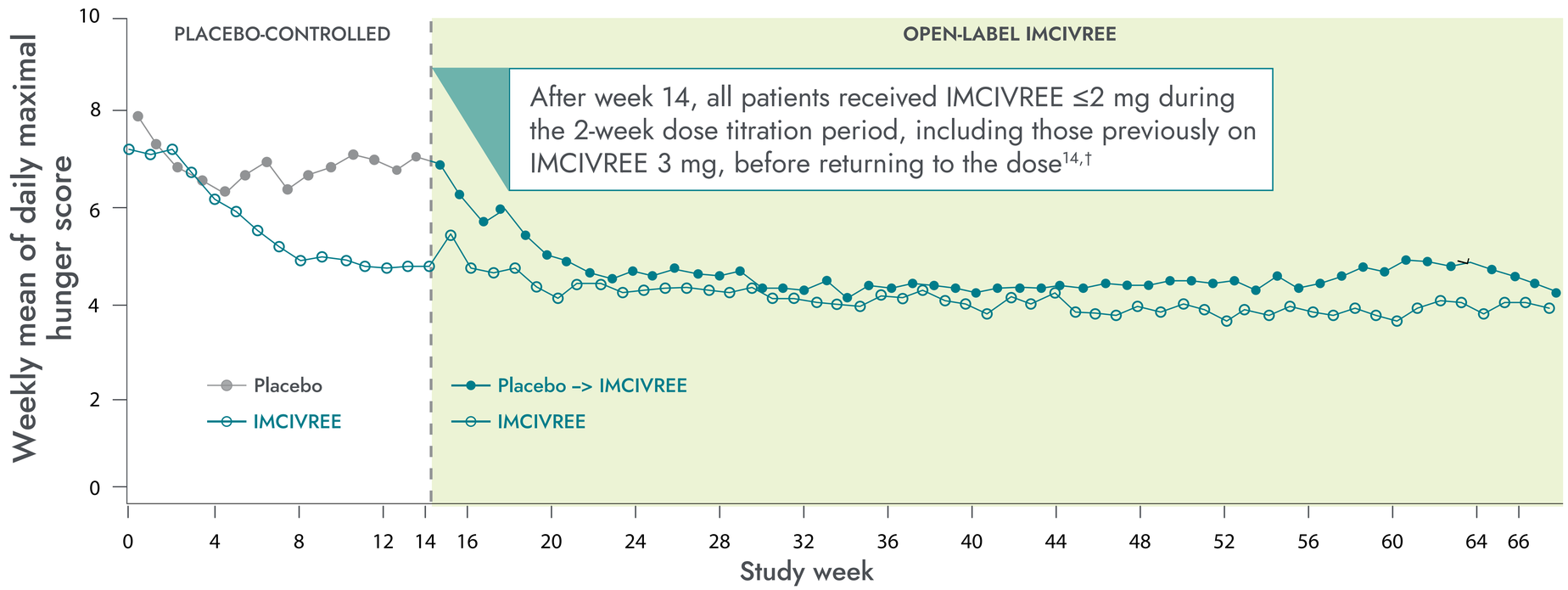
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥12 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED HUNGER REDUCTION[47]

Hunger scores in the 14-week placebo-controlled and 52-week open-label periods[1,47,*]



2.1-POINT REDUCTION in mean hunger score at week 52[1]

Caregiver assessments were also collected for children <12 with obesity due to BBS[48‡]

*Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible").[1]
†During the placebo-controlled period, dose titration to a fixed dose of IMCIVREE 3 mg given subcutaneously once daily was performed during the first 2 weeks of both the placebo-controlled and open-label periods to maintain blinding.[1]
‡Data not shown.

Patients who switched from placebo to IMCIVREE experienced a rapid reduction in hunger, matching that of patients initially assigned to IMCIVREE[1,50]

+ Hunger scale

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

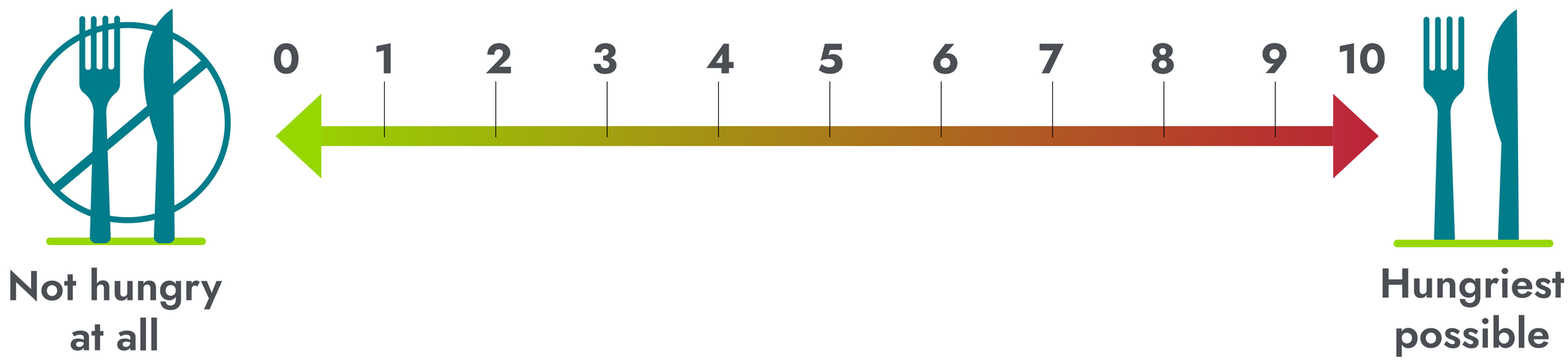
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥12 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED HUNGER REDUCTION[4,7]

HUNGER SCALE IN THE BBS CLINICAL TRIAL[1]



- Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2
- Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible")

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[47,53]

Key
- Primary trial data
- Long-term extension trial data

Clinically significant ~10% mean weight reduction in patients ≥18 years of age at week 52[47,53]

- At 24 months, patients in a long-term extension trial experienced an ~15% mean reduction in body weight[54]

+ 14-week weight reduction results vs placebo

+ 24-month long-term extension trial

Mean change in body weight in patients ≥18 years of age is an exploratory endpoint.[47]
*ATB=active treatment baseline, defined as the last measurement before the first dose of IMCIVREE, ie, week 0 for IMCIVREE group and week 14 for placebo group.[47]
†Data shown includes only patients who received 52 weeks of IMCIVREE at the time of the analysis.[47]
‡For patients aged 18 years or older, population sizes ranged from 7 to 15, with n=12 at 52 weeks on active treatment. Error bars are the standard deviation.[47]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Please see additional Important Safety Information and full Prescribing Information.

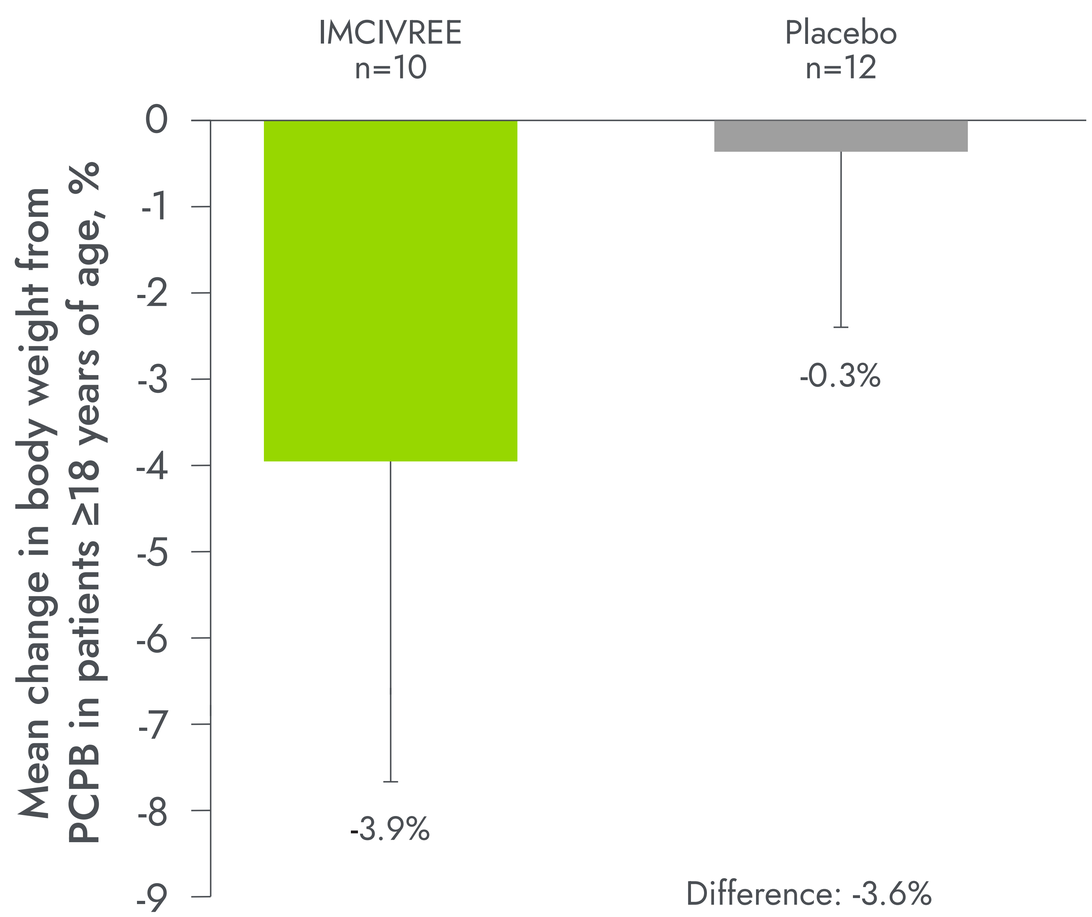
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥18 years of age with BBS

13X GREATER WEIGHT REDUCTION WITH IMCIVREE[47]

WEIGHT CHANGES IN PIVOTAL AND SUPPLEMENTAL PATIENTS ≥18 YEARS OF AGE WITH BBS DURING THE 14-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED PERIOD[47]*

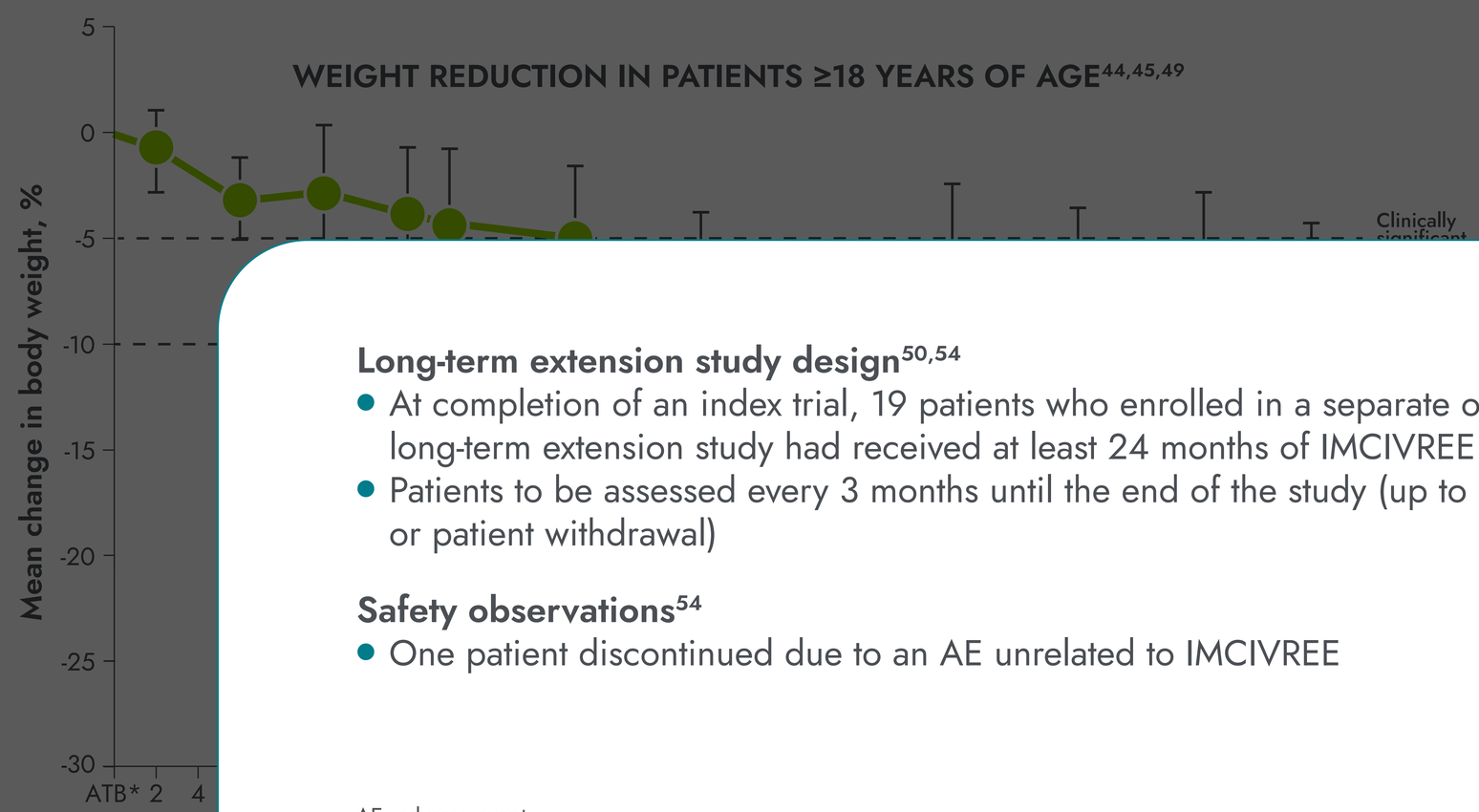


* Results in sub-population based on post hoc analysis. Supplemental patients were enrolled after the pivotal cohort had begun treatment. None of the supplemental patients had completed 52 weeks of IMCIVREE treatment at the time of data analysis.[47]

PCPB=placebo-controlled period baseline.

In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[44,45,48]



Key
- Primary trial data
- Long-term extension trial data

Long-term extension study design[50,54]

- At completion of an index trial, 19 patients who enrolled in a separate open-label, long-term extension study had received at least 24 months of IMCIVREE
- Patients to be assessed every 3 months until the end of the study (up to 5 years or patient withdrawal)

Safety observations[54]

- One patient discontinued due to an AE unrelated to IMCIVREE

AE=adverse event.

gnificant ~10% mean
uction in patients
f age at week 52[44,48]

s, patients in a long-term
al experienced an ~15%
ion in body weight[49]

veek weight reduction
lts vs placebo

month long-term
ension trial

Mean change in body weight in patients ≥18 years of age to an exploratory endpoint.
*ATB=active treatment baseline, defined as the last measurement before the first dose of IMCIVREE, ie, week 0 for IMCIVREE group and week 14 for placebo group.[44]
†Data shown includes only patients who received 52 weeks of IMCIVREE at the time of the analysis.[44]
‡For patients aged 18 years or older, population sizes ranged from 7 to 15, with n=12 at 52 weeks on active treatment. Error bars are the standard deviation.[44]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Please see additional Important Safety Information and full Prescribing Information.

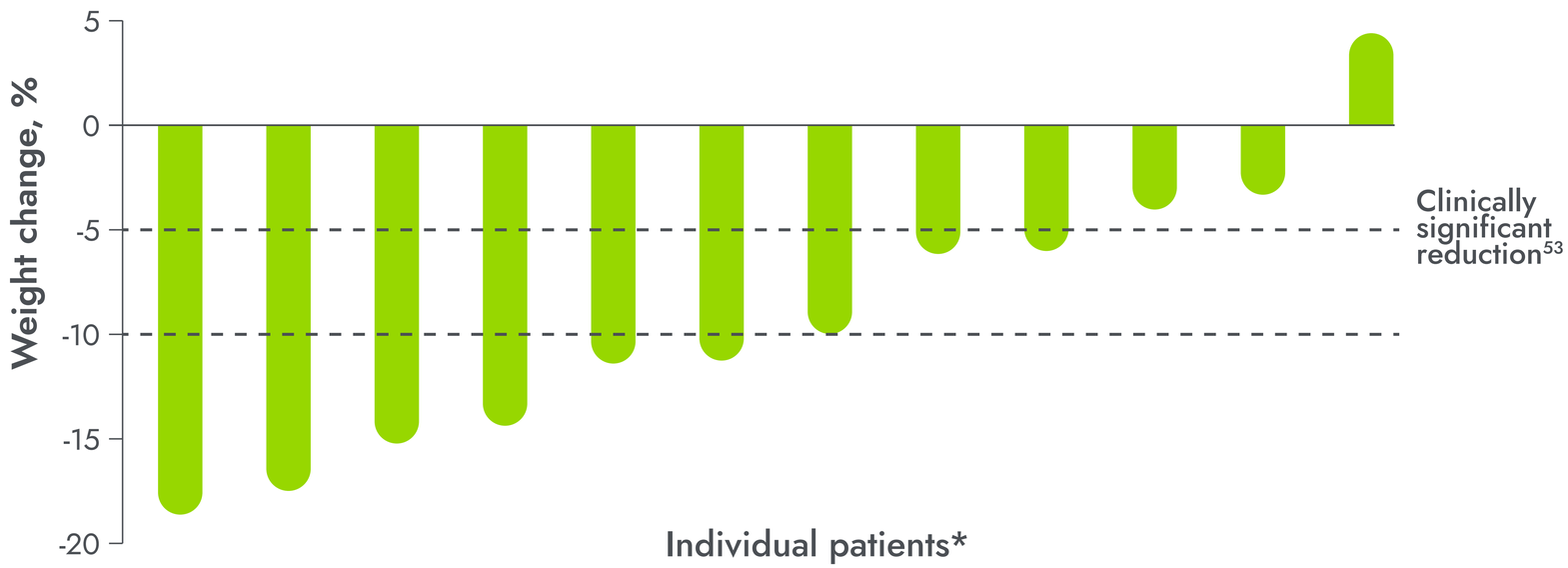
IMCIVREE®
(setmelanotide) injection

REFERENCES

In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[47,53]

PERCENTAGE CHANGE IN WEIGHT IN PATIENTS ≥18 YEARS OF AGE AFTER 52 WEEKS (n=12)[50]



Patients were not required to change their diet or exercise routine[50]

- **14-week weight reduction results vs placebo**
- **24-month long-term extension trial**

*Patients with data after 52 weeks of treatment.[50]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

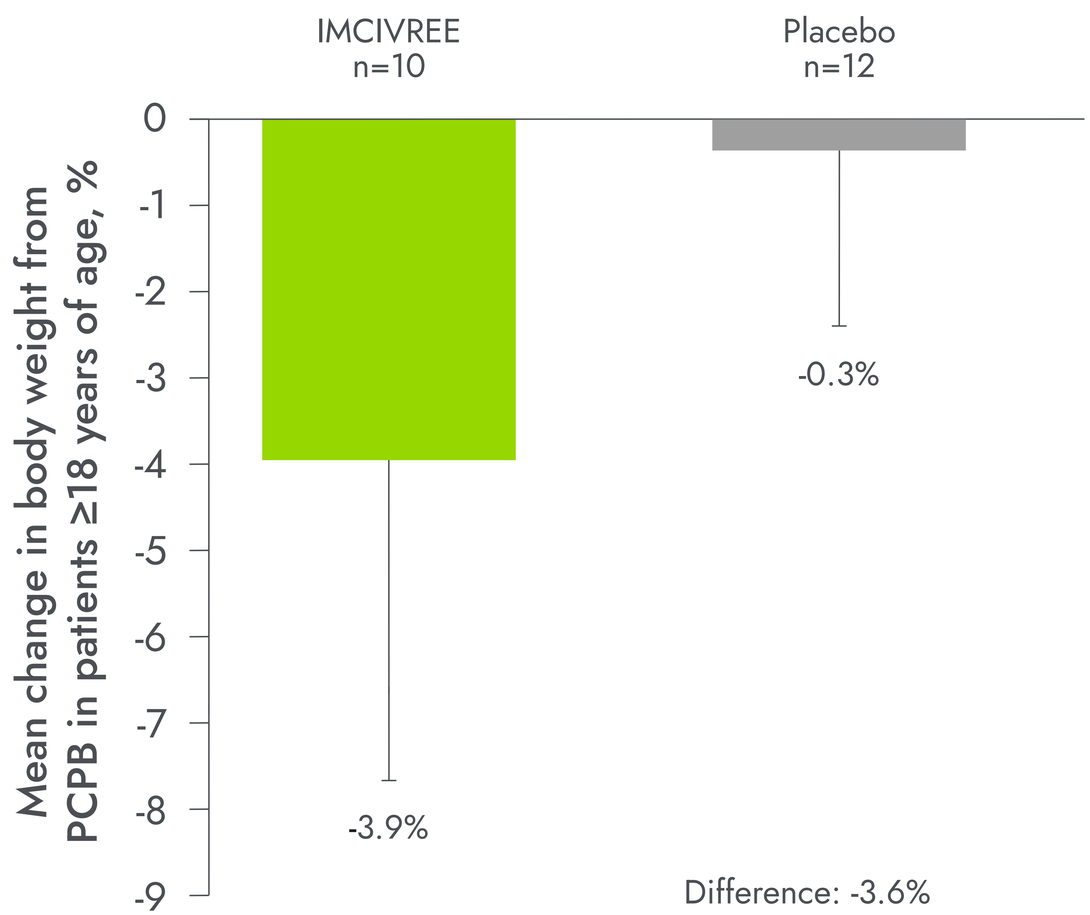
In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[44,45,48]

In patients ≥18 years of age with BBS

13X GREATER WEIGHT REDUCTION WITH IMCIVREE[47]

WEIGHT CHANGES IN PIVOTAL AND SUPPLEMENTAL PATIENTS ≥18 YEARS OF AGE WITH BBS DURING THE 14-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED PERIOD[47,*]



*Results in sub-population based on post hoc analysis. Supplemental patients were enrolled after the pivotal cohort had begun treatment. None of the supplemental patients had completed 52 weeks of IMCIVREE treatment at the time of data analysis.[47]

PCPB=placebo-controlled period baseline.

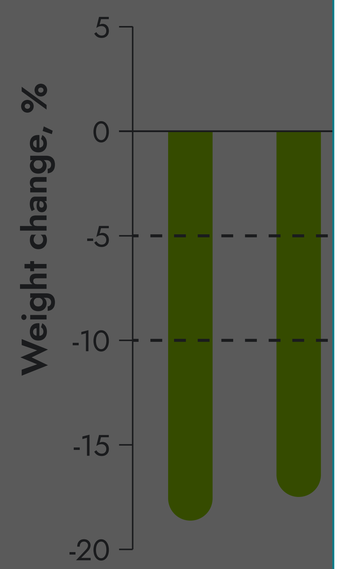
Please see additional Important Safety Information and full Prescribing Information.

REFERENCES

In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED WEIGHT REDUCTION[44,45,48]

WEIGHT REDUCTION | INDIVIDUAL RESULTS | CHANGE IN BMI | HUNGER REDUCTION | QUALITY OF LIFE



*Patients with data after 52 we

ot required
diet or
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k weight reduction
vs placebo

nth long-term
on trial

IMCIVREE DELIVERED SUSTAINED AND IMPROVED WEIGHT REDUCTION[54,*]

~15% mean reduction in body weight at 24 months[54]

- One patient discontinued due to an AE unrelated to IMCIVREE[54]

Long-term extension study design[50,54]

- At completion of an index trial, 19 patients who enrolled in a separate open-label, long-term extension study had received at least 24 months of IMCIVREE
- Patients to be assessed every 3 months until the end of the study (up to 5 years or patient withdrawal)

*BMI Z-score was an exploratory endpoint used to measure the reduction in BMI in children. Compared with measures at index trial baseline.[50]

AE=adverse event.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

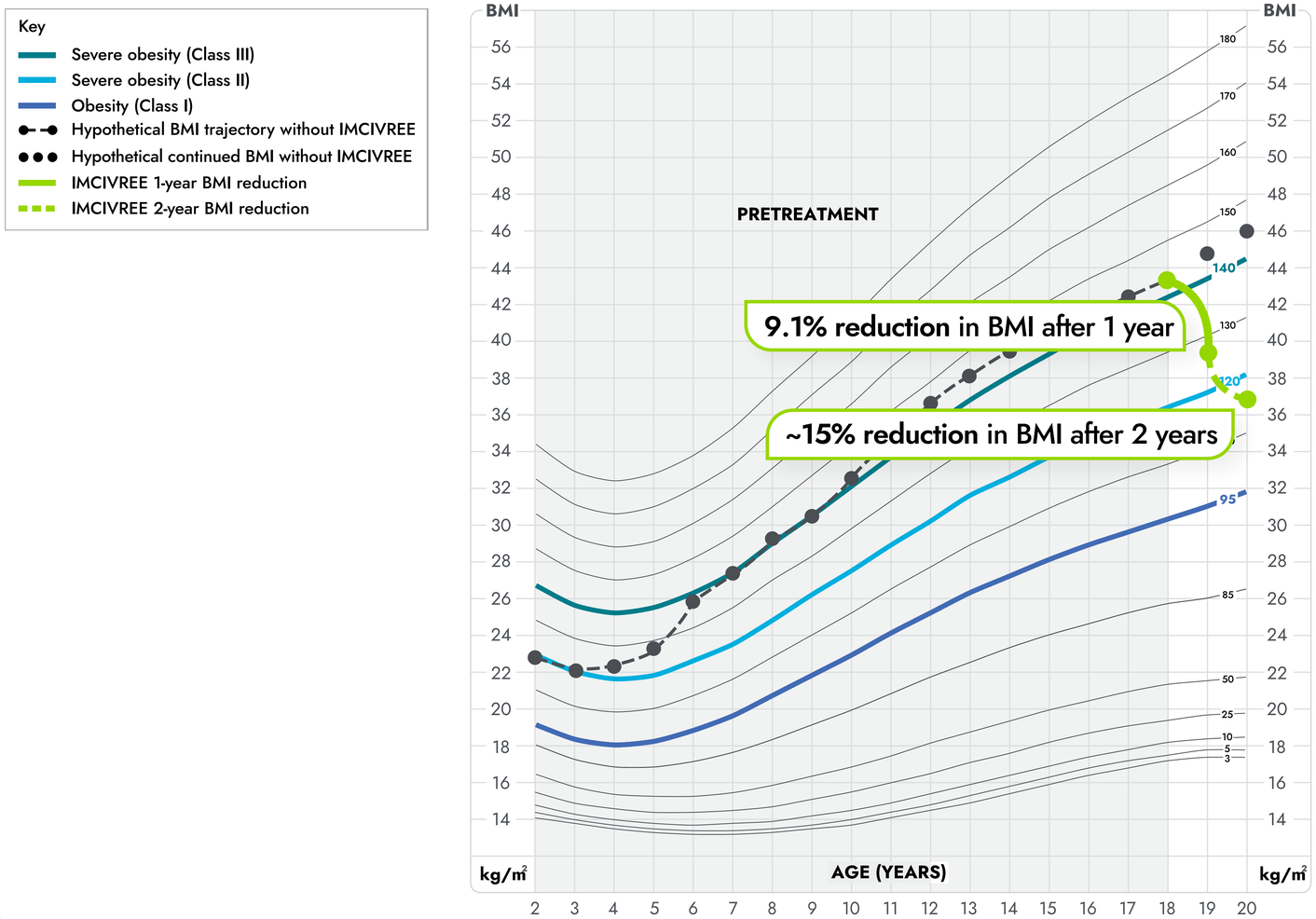
Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥18 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED REDUCTION IN BMI[47,53,54]



IMCIVREE SIGNIFICANTLY REDUCED THE SEVERITY OF OBESITY DUE TO BBS[47,53,54]

This chart is a visual representation of what a hypothetical adult with BBS* who started IMCIVREE at 18 years of age may experience in BMI reduction after 1 year and 2 years, based on data from the Phase 3 trial and a separate long-term extension trial[†‡]

*Not an actual patient.
[†]Patients with data after 1 year of treatment.[54]
[‡]Growth chart is based on females 2 to 20 years of age and is for illustrative purposes only. Figure modeled after Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. *Pediatrics*. 2012;130(6):1136-1140.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

Please see additional Important Safety Information and full Prescribing Information.

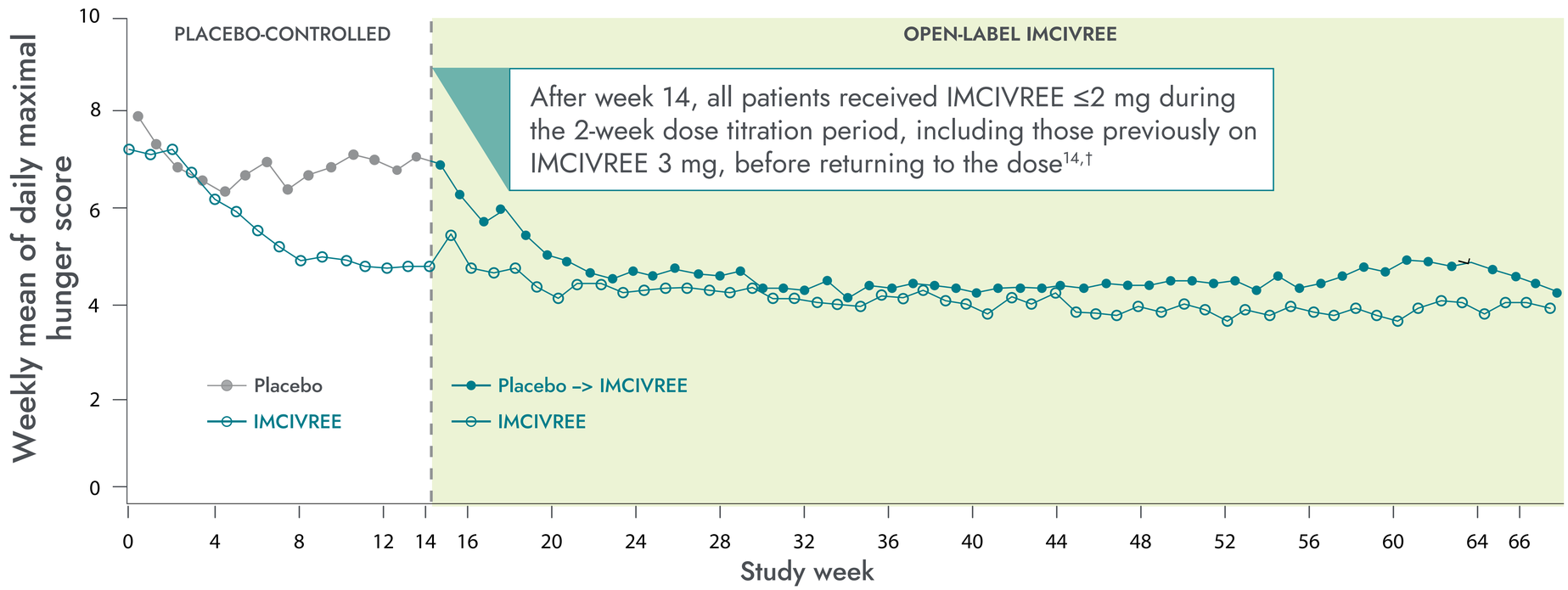
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥12 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED HUNGER REDUCTION[47]

Hunger scores in the 14-week placebo-controlled and 52-week open-label periods[1,47,*]



2.1-POINT REDUCTION in mean hunger score at week 52[1]

Caregiver assessments were also collected for children <12 with obesity due to BBS[48‡]

Patients who switched from placebo to IMCIVREE experienced a rapid reduction in hunger, matching that of patients initially assigned to IMCIVREE[1,50]

+ **Hunger scale**

*Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible").[1]

†During the placebo-controlled period, dose titration to a fixed dose of IMCIVREE 3 mg given subcutaneously once daily was performed during the first 2 weeks of both the placebo-controlled and open-label periods to maintain blinding.[1]

‡Data not shown.

Important Safety Information (cont'd)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

Please see additional Important Safety Information and full Prescribing Information.

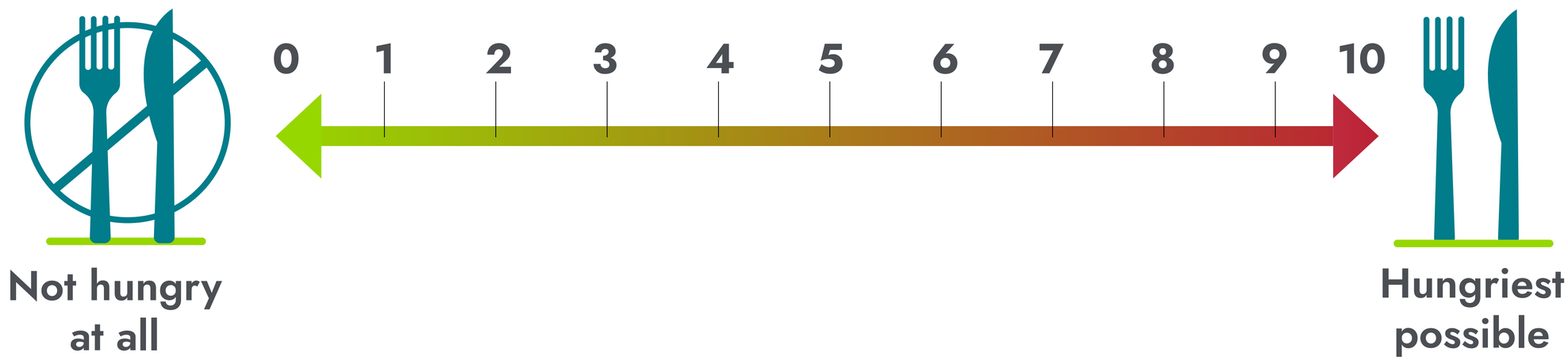
IMCIVREE® (setmelanotide) injection

REFERENCES

In patients ≥12 years of age with BBS

IMCIVREE DELIVERED EARLY, SIGNIFICANT, AND SUSTAINED HUNGER REDUCTION[4,5]

HUNGER SCALE IN THE BBS CLINICAL TRIAL[1]



- Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2
- Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible")

Important Safety Information (cont'd)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

Patient-Reported Health-Related Quality of Life

In the Phase 3 trial in patients 6 years and older with BBS, PedsQL and IWQOL-Lite were assessed as exploratory endpoints and were not powered for formal statistical testing or significance. Change from baseline after approximately 52 weeks of treatment was measured by the age-specific PedsQL or IWQOL-Lite assessments.[13]

- The PedsQL is a 23-item, self-reported, age-dependent assessment of health-related quality of life (HRQOL) in children and adolescents with or without acute or chronic health conditions that encompasses 4 domain scores: physical, emotional, social, and school functioning. The total score is the mean score of the transformed items across the 4 domains. The PedsQL was administered to children 6 to <18 years of age.[13,56]
- The Impact of Weight on Quality of Life (IWQOL)-Lite is a validated 31-item, self-reported, obesity-specific, quality-of-life questionnaire that provides a total score inclusive of 5 domains: physical function, self-esteem, sexual life, public distress, and work. The IWQOL-Lite was administered to patients ≥18 years of age.[13,57]

PedsQL Total Scores in Patients With BBS 6 to <18 Years Old With Baseline and Week 52 Data*[13]

	Baseline	Endpoint: Change From Baseline at Week 52
	All patients (n = 9)	All patients (n = 9)
PedsQL total score, mean (SD)	67.2 (18.9)	+11.2 (14.3)

IWQOL-Lite Total Scores in Patients With BBS ≥18 Years Old With Baseline and Week 52 Data[13]

	Baseline	Endpoint: Change From Baseline at Week 52
	All patients (n = 11)	All patients (n = 11)
IWQOL-Lite total score, mean (SD)	74.9 (12.0)	+12.0 (10.3)

- Raw scores for both PedsQL and IWQOL-Lite were transformed on a scale of 0–100, with 0 representing the worst possible and 100 the best possible HRQOL.[13]
- Limitations of these results include small sample sizes across assessments, which may be due in part to the rarity of the disease.[13]

HRQOL=Health-Related Quality Of Life; IWQOL-Lite=Impact of Weight on Quality Of Life-Lite; PedsQL=Pediatric Quality of Life Inventory.

*Using age-specific PedsQL or IWQOL-Lite assessments.

+ Patient and caregiver testimonials

+ Clinician testimonials

Important Safety Information

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

"Before IMCIVREE, I didn't realize how much time I spent focusing on food, and how much that was affecting my day-to-day and the other things I could be accomplishing."

— Kathryn, who is living with BBS

"The change in Reed's hunger has cascaded into many positive life changes for all of us. There's less agitation and anxiety over hunger or family meals. This is simple normalcy for many families, but for us, they're moments I'll never take for granted."

— Kat, caregiver of a child living with BBS

"He is no longer digging through the fridge or garbage, so we do not lock them anymore. He isn't asking for food constantly between meals and snacks, and I sometimes find myself realizing it's been a few hours and asking him if he's ready for a snack."

— Rachel, caregiver of a child living with BBS

Individual results may vary

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

IMCIVREE AND QUALITY OF LIFE

"Patients and families living with BBS often express such gratitude and relief when started on IMCIVREE and see the weight trajectories and hyperphagia start to improve. To have a medication that can support correcting the biology that is dysregulated and to see positive outcomes provides hope."

— Alaina Vidmar, Pediatric Endocrinologist

"These are patients that nothing else has ever worked. So to see them so happy about having something that's finally helping is amazing. Now all they talk about is, 'I'm not hungry all the time. I'm not seeking out food all the time. I'm able to do other things.' That shift from the number on the scale to the quality of life, I really love that."

— Christy Davis, Obesity and Weight Management Specialist

Individual results may vary

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE®
(setmelanotide) injection

IMCIVREE HAS A WELL-ESTABLISHED SAFETY AND TOLERABILITY PROFILE

ADVERSE REACTIONS OCCURRING IN 3 OR MORE IMCIVREE-TREATED PATIENTS 2 TO <6 YEARS OF AGE (N=12)[1]*

	(%)
Skin hyperpigmentation†	83
Injection site reactions‡	67
Vomiting	58
Nasopharyngitis	42
Melanocytic nevus‖	33
Fall	33
Fever	33
Upper respiratory tract infection	33
Cough	25
Diarrhea	25

*Safety analysis was conducted in 12 patients (7 with POMC or LEPR deficiency and 5 with BBS)
†Includes skin hyperpigmentation, ephelides, nail pigmentation, pigmentation lip, skin discoloration, gingival hyperpigmentation
‡Includes injection site bruising, pruritus, discoloration, erythema, induration, oedema, pain, urticaria
‖Includes new melanocyte nevus formation, increased melanocyte nevus size, and darkening of pre-existing melanocytic nevus

AE=adverse event.

AEs WERE GENERALLY MILD AND TRANSIENT[1,47,58]

In the clinical trial for patients 2 to <6 years of age:

- Reported incidences of vomiting primarily occurred within the first month of treatment. Vomiting was observed at a higher incidence in the study for patients 2 to <6 years of age compared with other IMCIVREE studies in patients 6 years of age and older
  - Nearly all vomiting events were mild, none were serious, and all resolved

Hyperpigmentation

Important Safety Information (cont'd)

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

IMCIVREE HAS A WELL-ESTABLISHED SAFETY AND TOLERABILITY PROFILE

ADVERSE REACTIONS OCCURING IN 2 OR MORE IMCIVREE-TREATED PATIENTS 6 YEARS OF AGE AND OLDER (N=43)[1,*]

	(%)
Skin hyperpigmentation[†]	63
Injection site reactions[‡]	51
Nausea	26
Spontaneous penile erection[§]	25
Vomiting	19
Diarrhea	14
Melanocytic nevus[‖]	14
Headache	7
Skin striae	7
Aggression	5
Fatigue	5

*Forty three patients were treated with at least 1 dose of IMCIVREE; 1 patient initially randomized to placebo withdrew from the study prior to receiving IMCIVREE and is not included.[1]
[†]Includes skin hyperpigmentation, hair color changes, melanoderma
[‡]Includes injection site erythema, pruritus, induration, pain, bruising, edema, reaction, hemorrhage, irritation, mass.[1]
[§]n=20 male patients.[1]
[‖]Includes new melanocytic nevus formation, increased melanocytic nevus size, and darkening of pre-existing melanocytic nevus
AE=adverse event.

AEs WERE GENERALLY MILD AND TRANSIENT[47]

In the clinical trial for patients 6 years of age and older:

- Reported incidences of nausea and vomiting primarily occurred within the first month of treatment, then sharply declined after 4 weeks[50]
  - Nearly all nausea or vomiting events were mild, none were serious, and all typically resolved within a few days[50,54]
  - Nausea and vomiting should be managed by dose titration and standard care[1]

The safety of IMCIVREE has been evaluated in over 700 patients over 10+ years

+ Hyperpigmentation

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

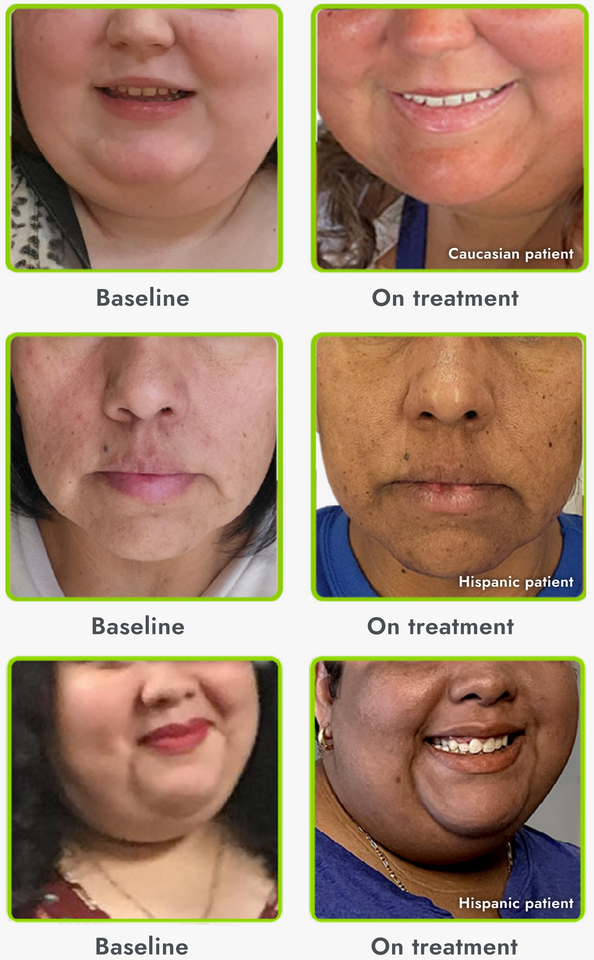
Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

HYPERPIGMENTATION IS COMMON[1,47]

Examples of hyperpigmentation[45]



Baseline | On treatment
Baseline | On treatment
Baseline | On treatment

- IMCIVREE is an MC4R agonist, but has some residual activity at the MC1R which commonly leads to hyperpigmentation[1,47]
- The activation of the MC1 receptor leads to accumulation of melanin which leads to hyperpigmentation[1]
- The degree of hyperpigmentation is highly variable[59]
- In clinical trials, measures of hyperpigmentation increased throughout the dose escalation period and generally plateaued in the initial months of treatment[47]
- Hyperpigmentation is reversible after treatment discontinuation[1]
- If hyperpigmentation is a concern, assess patient response to treatment to optimize tolerability and efficacy as you would with other adverse events

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

WARNINGS AND PRECAUTIONS[1]

Indication

IMCIVREE is indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS).

Limitations of Use

IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- Other types of obesity not related to BBS or other FDA-approved indications for IMCIVREE, including obesity associated with other genetic syndromes and general (polygenic) obesity

Important Safety Information

CONTRAINDICATIONS

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see the full Prescribing Information for additional Important Safety Information.

IMCIVREE®
(setmelanotide) injection

ONCE-DAILY, SUBCUTANEOUS INJECTION THAT CAN BE ADMINISTERED AT HOME[1]

DOSING | SETTING EXPECTATIONS

Titrate patients to the maintenance dose to optimize efficacy and tolerability

	Starting dose (Weeks 0-2)	Uptitration dose	Recommended maintenance dose by body weight
Young Children (2 to <6 years of age)	**0.5 mg** once daily	**0.5 mg** once daily (Every 1-2 weeks increase dose by 0.5 mg until recommended dose by body weight)	**0.5 mg** once daily for 15 to <20 kg (33-44 lbs) **1.0 mg** once daily for 20 to <30 kg (44-66 lbs) **1.5 mg** once daily for 30 to <40 kg (66-88 lbs) **2.0 mg** once daily for ≥40 kg (88 lbs)

When the child reaches age 6, the maintenance dose increases to 3 mg

	Starting dose (Weeks 0-2)	Uptitration dose	Recommended maintenance dose
Children (6 to <12 years of age)	**1 mg** once daily	**2 mg** once daily	**3 mg** once daily

	Starting dose (Weeks 0-2)	Recommended maintenance dose
Children and adults (≥12 years of age)	**2 mg** once daily	**3 mg** once daily

+ Dosing for severe renal impairment

- IMCIVREE should be administered once daily, at the beginning of the day, without regard to meals
  - There is no food requirement for administration
- No dose adjustments are needed for patients with mild to moderate renal impairment

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

IMCIVREE is not recommended for use in patients with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2)[1]

Recommended dosage in patients with severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m^2)[1]

For patients aged 2 to <6 weighing at least 20 kg with severe renal impairment:

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 2 to less than 6 years with severe renal impairment and weight at least 20 kg
- **The use of IMCIVREE in pediatric patients aged 2 to less than 6 years with weight less than 20 kg and severe renal impairment is not recommended**
- Monitor patients for GI adverse reactions during dosage initiation and titration
- If the recommended starting dosage is:
  - Not tolerated; discontinue IMCIVREE
  - Tolerated for 2 weeks; increase the dosage based on baseline body weight, as presented in the table below

Recommended Maintenance Dosage Based on Baseline Body Weight in Pediatric Patients 2 to Less Than 6 Years of Age Weighing at Least 20 kg and with Severe Renal Impairment

Patient Weight/Treatment Week	Daily Dose	Volume to be Injected
20 kg to less than 30 kg		
Week 1 and onward	0.5 mg once daily	0.05 mL once daily
30 kg to less than 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Week 3 and onward	1 mg once daily	0.1 mL once daily
Greater than or equal to 40 kg		
Weeks 1-2	0.5 mg once daily	0.05 mL once daily
Week 3 and onward	1 mg once daily	0.1 mL once daily

- The recommended maintenance dosage is 1 mg (0.1 mL) injected subcutaneously once daily. Monitor patients for adverse reactions

eGFR=estimated glomerular filtration rate; GI=gastrointestinal.

persistent depression symptoms occur.

Please see additional Important Safety Information and full Prescribing Information.

(setmelanotide) injection

REFERENCES

IMCIVREE is not recommended for use in patients with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2)[1]

For patients aged 6 to <12 with severe renal impairment:

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in pediatric patients aged 6 to less than 12 years with severe renal impairment
- Monitor patients for GI adverse reactions during dosage initiation and titration
- If the recommended starting dosage is:
  - Not tolerated; discontinue IMCIVREE
  - Tolerated to 2 weeks, increase the dosage to 1 mg (0.1 mL) injected subcutaneously once daily. The recommended maintenance dosage is 1 mg (0.1 mL) injected subcutaneously once daily

For patients aged ≥12 with severe renal impairment:

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks in adults and pediatric patients aged 12 years and older with severe renal impairment
- Monitor patients for GI adverse reactions during dosage initiation and titration
- If the recommended starting dosage is:
  - Not tolerated; discontinue IMCIVREE
  - Tolerated for 2 weeks; increase the dosage to 1 mg (0.1 mL) once daily. If the 1 mg daily dosage is tolerated for at least 1 week, increase the dosage to 1.5 mg (0.15 mL) once daily. The recommended maintenance dosage is 1.5 mg (0.15 mL) injected subcutaneously once daily.

There is no recommended dosage change in patients with mild or moderate renal impairment[1]

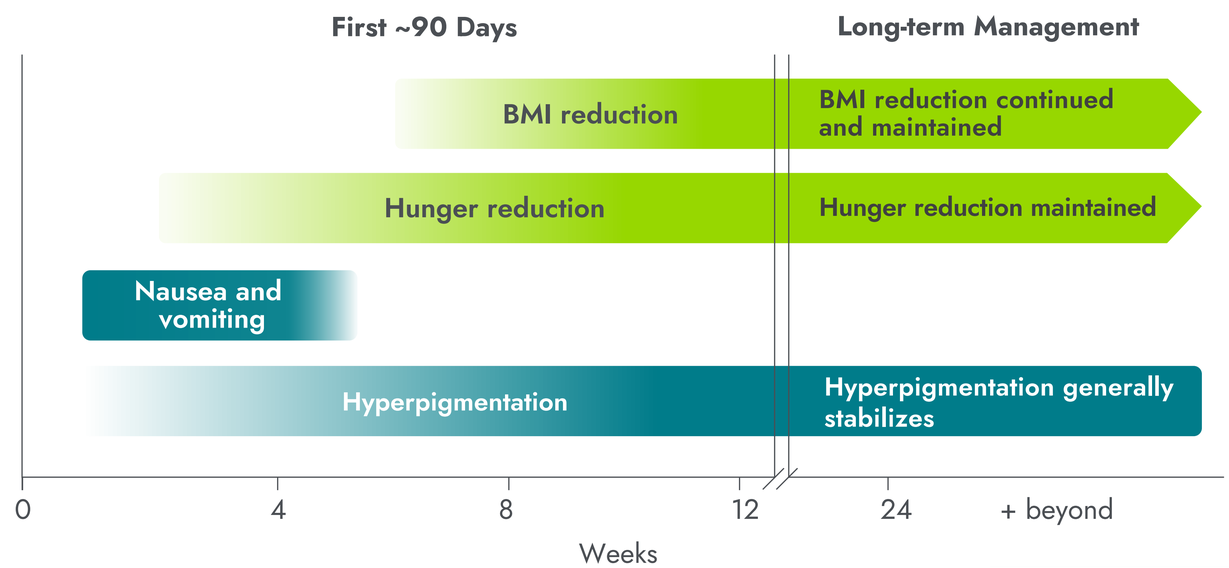
- The recommended dosage in patients with mild renal impairment (eGFR of 60 to 89 mL/min/1.73 m^2) or moderate renal impairment (eGFR of 30 to 59 mL/min/1.73 m^2) is the same as in those with normal kidney function

eGFR=estimated glomerular filtration rate; GI=gastrointestinal.

EFFECTIVE, LONG-TERM WEIGHT MANAGEMENT STARTS WITH SETTING PATIENT EXPECTATIONS

Achieving the benefits of treatment with IMCIVREE may take time

In clinical trials, it took some time for hunger and weight reductions to occur, while patients experienced certain AEs soon after starting treatment. This chart highlights some of the most common AEs, but it does not include all reported AEs.



AE=adverse event.

Managing patient expectations

In clinical trials:

- **Meaningful weight reduction** began within 6-8 weeks and continued over time[1,47,48,53,54]
- **Hunger reduction** began within weeks. Measures of hunger increased quickly upon dose reduction or discontinuation of IMCIVREE[1,47,48,50,60]
- **Nausea and vomiting** were primarily reported within the first 4 weeks of treatment and typically resolved within a few days; nearly all events were mild and none were serious [47,48,50,54]
- **Hyperpigmentation** typically occurred within 2-3 weeks and increased throughout the dose titration period; levels generally plateaued in the initial months of treatment and were sustained over long-term treatment with IMCIVREE[50]

Talking to patients about when they can expect weight and hunger benefits and common adverse reactions may help them manage through the short-term treatment initiation to achieve their longer-term goals

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

GETTING YOUR PATIENT STARTED ON IMCIVREE

3 simple steps to initiate treatment:

1. Download the **IMCIVREE Prescription Start Form** to start prescribing at IMCIVREE.com/start
   - The preferred method of starting IMCIVREE is via our Prescription Start Form

     If you would prefer to e-prescribe, please be sure to select PANTHERx Rare Pharmacy
   - This form serves as your patient's prescription and provides an opportunity for your patient to enroll in Rhythm InTune, a support program from Rhythm Pharmaceuticals
2. Follow the instructions to complete the form
3. Submit all pages of the completed form via fax to **1-877-805-0130** or email **patientsupport@rhythmtx.com**

IMCIVREE is only available through PANTHERx Rare Pharmacy*

Financial assistance may be available to eligible patients for whom IMCIVREE treatment is indicated. For questions on IMCIVREE or how to start a patient, call Rhythm InTune at **1-855-206-0815** Monday – Friday, 8 AM to 8 PM ET.

*In Puerto Rico, IMCIVREE is only available through Special Care Pharmacy Services

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

Rhythm InTune
Support made personal

RHYTHM INTUNE IS A SUPPORT PROGRAM DESIGNED FOR CAREGIVERS AND INDIVIDUALS LIVING WITH RARE DISEASES OF OBESITY, INCLUDING BBS

RHYTHM INTUNE | PATIENT ACCESS

A Rhythm InTune Patient Education Manager* can help people living with BBS and their caregivers:

- **Access educational resources,** such as virtual education programs about BBS or treatment with IMCIVREE.
- **Connect to a community** where they can learn from other people living with BBS, their caregivers, and clinical experts
- **Understand their insurance coverage** and navigate the approval process
- **Get started on treatment** by coordinating IMCIVREE deliveries and injection support and training with the specialty pharmacy.
- **With wellness tips and a framework for tracking success†**

*Patient Education Managers are employees of Rhythm Pharmaceuticals and do not provide medical care or advice. We encourage your patients to always speak to their healthcare providers regarding their medical care.

†Designed to support patients and caregivers as they work with their doctor on wellness goals.

Rhythm InTune offers personalized support through a single point of contact that's here for patients as they navigate their BBS journey.

For more information about the services Rhythm InTune provides, contact us at:

patientsupport@rhythmtx.com

1-855-206-0815

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE®
(setmelanotide) injection

RHYTHM IS COMMITTED TO PATIENT ACCESS AND SUPPORT

RHYTHM INTUNE IS COMMITTED TO ASSISTING ELIGIBLE PATIENTS, REGARDLESS OF INSURANCE PLAN TYPE

The majority of patients, regardless of coverage type, have obtained approval for IMCIVREE[50]

- Many patients have obtained coverage approval at the prior authorization level
- The majority of commercial plans have coverage policies in place for IMCIVREE
- The majority of Medicaid-covered lives have a coverage policy in place or a positive decision on IMCIVREE coverage

Financial assistance programs are available for eligible patients

Actor portrayal.

Important Safety Information (cont'd)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE®
(setmelanotide) injection

REFERENCES

IMCIVREE IS THE FIRST AND ONLY PRECISION MEDICINE TO TARGET IMPAIRMENT OF THE HYPOTHALAMIC MC4R PATHWAY, A ROOT CAUSE OF HYPERPHAGIA AND OBESITY IN BBS[1,2]

The MC4R pathway is a key pathway in the hypothalamus that regulates hunger and energy expenditure[2]

People living with BBS can have a genetic variant that impairs the MC4R pathway, a root cause of hyperphagia and early-onset obesity

IMCIVREE, an MC4R agonist, acts in place of alpha—melanocyte-stimulating hormone (α-MSH) to activate the MC4 receptor, and help re-establish MC4R pathway activity[1,4,18]

IMCIVREE delivered early and clinically meaningful weight reduction in people aged 2 years and older in BBS clinical trials[1,47,48]

IMCIVREE is foundational to the long-term treatment of obesity due to BBS as the only precision medicine designed to re-establish MC4R pathway activity. This pathway activity is critical to maintain regulated satiety signaling, energy expenditure, and weight.[1]

IMCIVREE has a well-established safety and tolerability profile[1,48,54]

MC4R=melanocortin-4 receptor.

> "Hunger and obesity ruled Reed's life, so it ruled ours, too. The impact of IMCIVREE has been transformational for Reed's weight, and also for our family."
>
> *— Kat, caregiver of a child living with BBS*

Individual results may vary

Get your patients started on IMCIVREE today with the Prescription Start Form at IMCIVREE.com/start

Indication

IMCIVREE is indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS).

Learn more about genetic testing that can help inform your diagnosis of BBS ▶

Access the Diagnosing BBS Tool ▶

Important Safety Information

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Please see additional Important Safety Information and full Prescribing Information.

IMCIVREE® (setmelanotide) injection

REFERENCES

Overview | Mechanism of Action | Study Design | Efficacy: Aged 2 to <6 | Efficacy: Aged 6 to <18 | Efficacy: Aged ≥18 | Safety Profile: Aged 2 to <6 | Safety Profile: Aged ≥6 | Dosing and Administration | Prescribing IMCIVREE | Rhythm InTune | Summary

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Rhythm® PHARMACEUTICALS

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