IMCIVREE®
(setmelanotide) injection

What to expect when starting a patient on IMCIVREE

The **FIRST** and **ONLY** treatment to target impairment in the MC4R pathway, a root cause of hyperphagia and obesity in Bardet-Biedl syndrome (BBS)[1,2]

MC4R=melanocortin-4 receptor

Indication

IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to Bardet-Biedl syndrome (BBS).

Limitations of Use

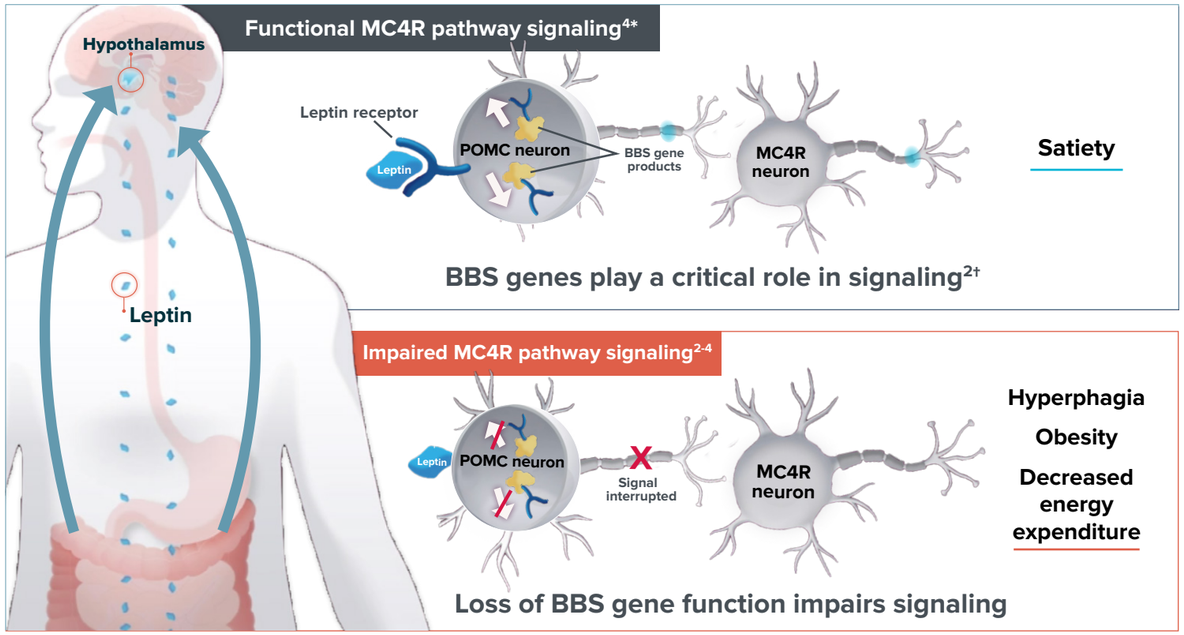
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- 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

Please see additional Important Safety Information on page 13 and full Prescribing Information.

Impairment in the MC4R pathway is a root cause of obesity and hyperphagia in BBS[2]

The MC4R pathway is a key signaling pathway that regulates hunger, satiety, and energy expenditure[2,3]



*Functional MC4R pathway signaling is activated by leptin, a neurosignaling hormone generated in adipose tissue.[2,3]
†BBS genes help traffic leptin receptors to the cell surface of POMC neurons, which can activate MC4R neurons.[2-4]

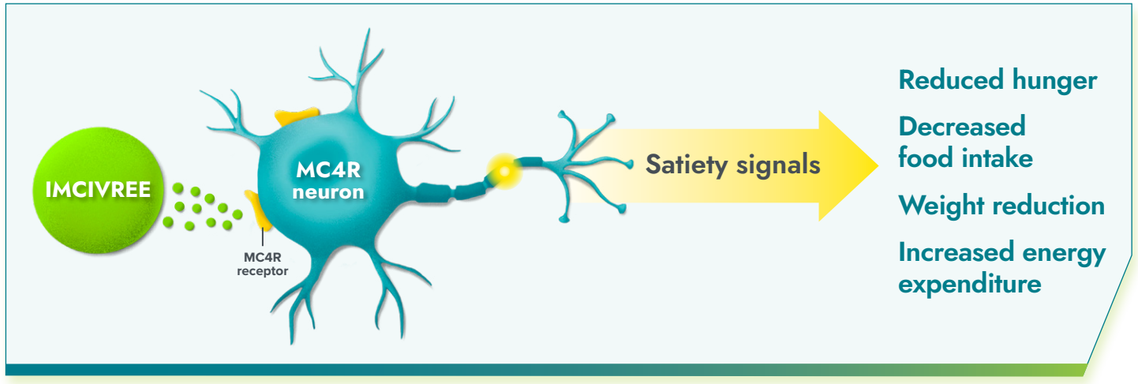
POMC=pro-opiomelanocortin.

IMCIVREE® (setmelanotide) injection

Please see additional Important Safety Information on page 13 and full Prescribing Information.

IMCIVREE is the first and only treatment to target impairment in the MC4R pathway, a root cause of obesity and hyperphagia in BBS[1,2]

IMCIVREE, an MC4R agonist, is designed to re-establish MC4R pathway activity[1]



Important Safety Information

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.

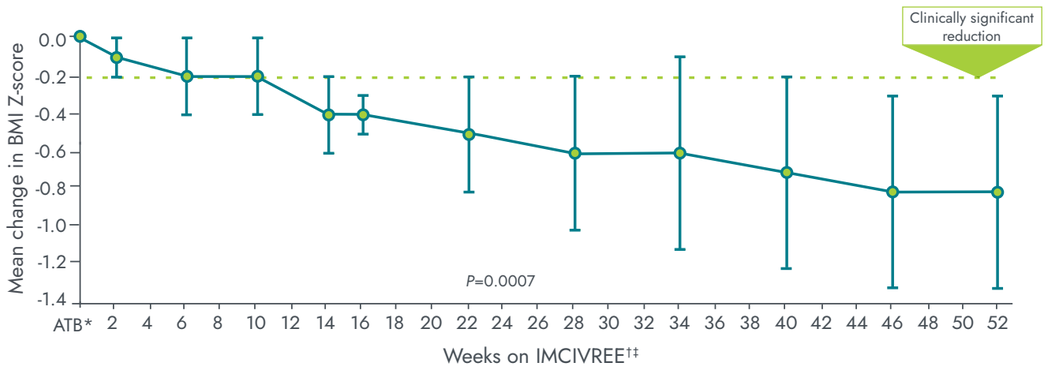
IMCIVREE delivered BMI reductions[1]

- ~8% mean reduction in BMI in patients ≥6 years of age after 1 year

In patients <18 years of age with BBS

IMCIVREE delivered early, significant, and sustained reduction in BMI Z-score[5]

BMI Z-score reduction in patients <18 years of age[5]*



- Clinically significant -0.8 mean change in BMI Z-score[5]
  - 100% of patients <12 years of age achieved a clinically significant ≥0.2 reduction in BMI Z-score (n=3)[5,6§]

Study design: The efficacy and safety of IMCIVREE for the reduction of weight and hunger in patients with BBS were studied in a 66-week phase 3 clinical trial, which included a 14-week randomized, double-blind, placebo-controlled period and a 52-week open-label period. The study enrolled patients aged 6 years and older with obesity and a clinical diagnosis of BBS.[1,7]

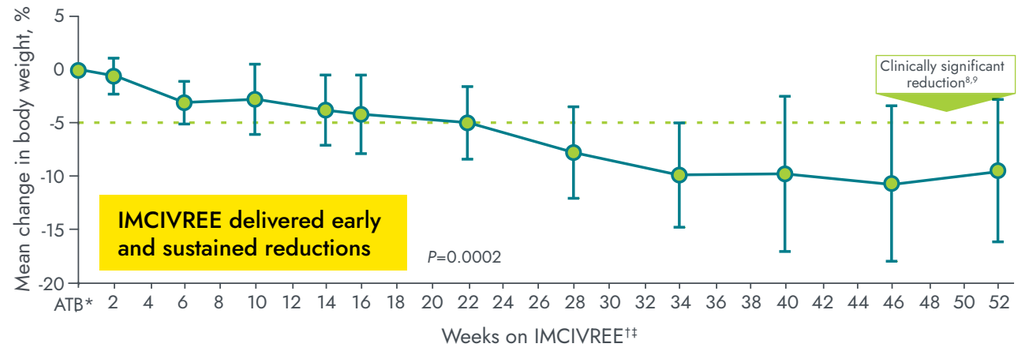
IMCIVREE® (setmelanotide) injection

Please see additional Important Safety Information on page 13 and full Prescribing Information.

In patients ≥18 years of age with BBS

IMCIVREE provided clinically significant weight reduction[5]

Weight reduction in patients ≥18 years of age[5]



- Clinically significant **~10%** mean weight reduction in patients ≥18 years of age[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.[5]
†Data shown only include patients who received 52 weeks of IMCIVREE at the time of the analysis.[5]
‡For patients aged 18 years or older, population sizes range from 7 to 15, with n=12 at 52 weeks on active treatment. For patients aged <18 years, population sizes range from 8 to 16, with n=14 at 52 weeks on active treatment. Error bars are the standard deviation (SD).[5]
§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%.[6]

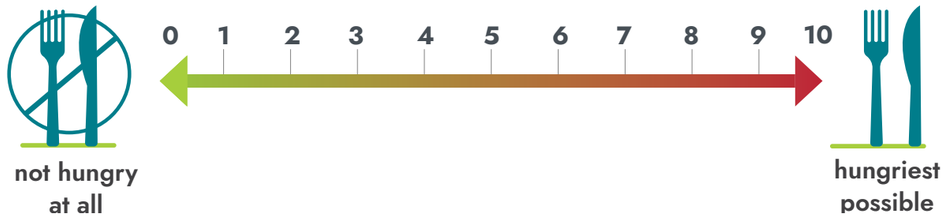
Patients were not required to change their diet or exercise routine[5]

Important Safety Information (cont'd)

Depression and Suicidal Ideation: Depression and suicidal ideation 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.

Measuring hunger[1]

Hunger scale in the BBS clinical trial[1]

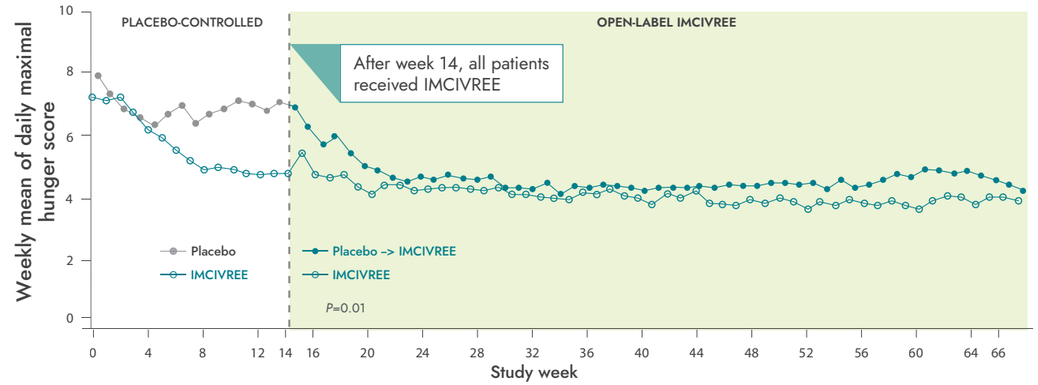


- Patients ≥12 years of age who were able to self-report their hunger (n=14) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2
- Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible")

> I don't feel like I have to crave food all the time anymore, which feels really good.
>
> *— An IMCIVREE-treated patient from the BBS clinical trial[5]*

IMCIVREE delivered early, significant, and sustained hunger reduction

Hunger scores in the 14-week placebo-controlled and 52-week open-label periods[5]



- 2.1-point reduction in mean hunger score after 52 weeks of treatment[1]

> Before the trial, according to her, she had never experienced not being hungry. After she started the trial, she wasn't even finishing her meals. She was full a lot faster where she had never left food on her plate before...
>
> *— Caregiver of an IMCIVREE-treated patient from the BBS clinical trial[5]*

PCPB=placebo-controlled period baseline.

IMCIVREE® (setmelanotide) injection

Please see additional Important Safety Information on page 13 and full Prescribing Information.

Important Safety Information (cont'd)

Skin Pigmentation and Darkening of Pre-Existing Nevi: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

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

Adverse reactions occurring in 2 or more IMCIVREE-treated patients (n=43*)[1]

	%
Hyperpigmentation disorders†	63
Injection site reactions‡	51
Nausea	26
Spontaneous penile erection§	25
Vomiting	19
Diarrhea	14
Headache	7
Skin striae	7
Aggression	5
Fatigue	5

*43 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.
†Includes skin hyperpigmentation, hair color changes, melanoderma, melanocytic nevus.
‡Includes injection site erythema, pruritis, induration, pain, bruising, edema, reaction, hemorrhage, irritation, mass.
§n=20 male patients.

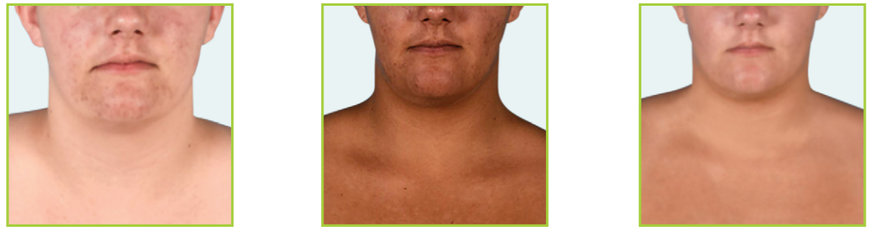
- Reported incidences of nausea and vomiting primarily occurred within the first month of treatment, then sharply declined after 4 weeks[5]
  - Nearly all nausea or vomiting events were mild and none were serious[5]
  - Reported incidences of nausea and vomiting typically resolved within a few days in patients with a rare genetic disease of obesity in IMCIVREE clinical trials[10]
  - Nausea and vomiting should be managed by dose titration and standard care[1]
- Adverse events (AEs) were generally mild and transient[5]
- No serious AEs related to IMCIVREE were reported in the BBS trial[5]

IMCIVREE® (setmelanotide) injection

Please see additional Important Safety Information on page 13 and full Prescribing Information.

Hyperpigmentation was common and rarely led to discontinuation[1,5]

Example of hyperpigmentation[11]

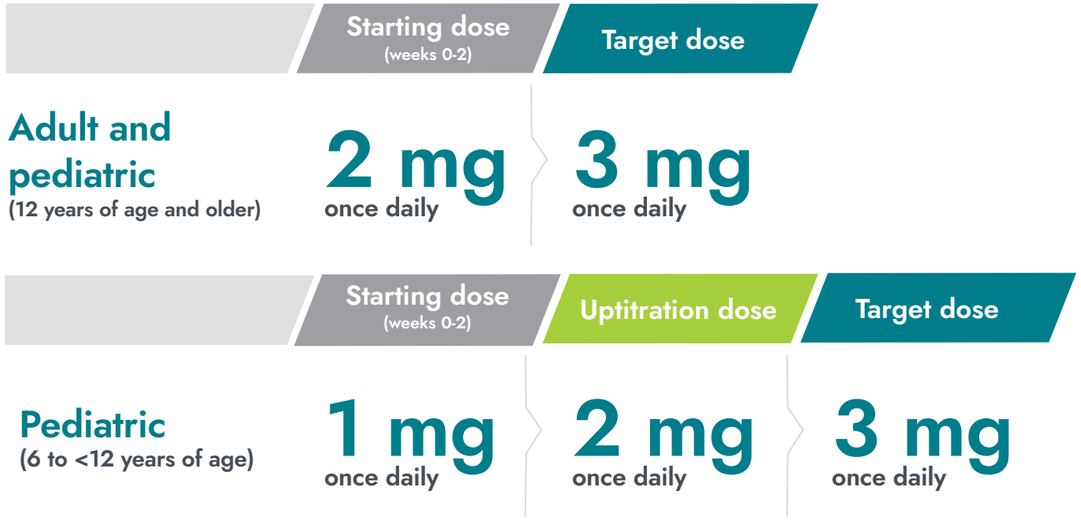


Baseline | After treatment | Following study

- Changes in skin pigmentation or hair color typically presented 2-3 weeks after initiation of IMCIVREE, with most events occurring within the first month of treatment[5]
  - Skin darkening plateaued within the initial months of treatment[5]
  - Hyperpigmentation is variable[11]
  - This effect is reversible upon discontinuation of treatment[1]
  - Perform a full body skin examination prior to starting and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions[1]
- **There were no reports of melanoma related to the observed hyperpigmentation in clinical trials of IMCIVREE[5]**
  - Hyperpigmentation is not unexpected given that IMCIVREE activates the melanocortin-1 receptor, which results in melanin production[1]

Once-daily, subcutaneous injection that can be administered at home[1]

Titrate IMCIVREE to the target dose[1]



- IMCIVREE should be administered once daily, at the beginning of the day, without regard to meals[1]
  - There is no food requirement for administration
- No dose adjustments are needed for patients with mild to moderate renal impairment[1]
  - Refer to the Prescribing Information for dose adjustments for patients with severe renal impairment

Dose should be titrated to optimize tolerability and response[1]

References: 1. IMCIVREE [prescribing information]. Boston, MA. Rhythm Pharmaceuticals, Inc. **2.** Eneli I et al. *Appl Clin Genet.* 2019;12:87-93. **3.** Huvenne H et al. *Obes Facts.* 2016;9(3):158-173. **4.** Seo S et al. *Hum Mol Genet.* 2009;18(7):1323-1331. **5.** Data on file. Rhythm Pharmaceuticals, Inc. Boston, MA. **6.** Grossman DC et al; US Preventive Services Task Force. *JAMA.* 2017;317(23):2417-2426. **7.** Haws RM et al. *Contemp Clin Trials Commun.* 2021;22:100780. **8.** American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. *Obesity (Silver Spring).* 2014;22 Suppl 2:S5-39. doi:10.1002/oby.20821. **9.** Williamson DA et al. *Obesity (Silver Spring).* 2015;23(12):2319-2320. **10.** Argente J et al. The Pediatric Endocrine Society Annual Meeting. Poster 155. April 28-May 1, 2022. **11.** Clément K et al. *Lancet Diabetes Endocrinol.* [Supplementary appendix] 2020;8(12):960-970.

IMCIVREE® (setmelanotide) injection

Please see additional Important Safety Information on page 13 and full Prescribing Information.

Getting your patients started on IMCIVREE

3 simple steps to initiate treatment

1. Download the IMCIVREE Start Form*
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**

*The preferred method of starting IMCIVREE is via our Start Form. If you would prefer to e-prescribe, please contact PANTHERx Rare Pharmacy.

IMCIVREE is only available through our specialty pharmacy†

†PANTHERx Rare Pharmacy.

Financial support 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.

Important Safety Information (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.

Rhythm InTune
Support made personal

A support program designed for caregivers and people living with BBS

A Rhythm InTune Patient Education Manager is a single point of contact who can help patients and caregivers:

Access educational resources, such as virtual education programs about BBS or treatment with IMCIVREE® (setmelanotide) injection.

Connect to a community where they can learn from the experiences of others.

Access treatment by helping with understanding drug coverage, prior authorizations, appeals support, and, for eligible patients, copay support and financial assistance.

Get started on treatment by coordinating IMCIVREE deliveries and injection support with the specialty pharmacy.

Rhythm InTune is committed to helping your patients access treatment with IMCIVREE

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

patientsupport@rhythmtx.com

1-855-206-0815

Important Safety Information

Indication

IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic 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

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 and suicidal ideation 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.

Skin Pigmentation and Darkening of Pre-Existing Nevi: Generalized increased skin pigmentation and darkening of pre-existing 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.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at 833-789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

IMCIVREE is the first and only treatment to target impairment in the MC4R pathway, a root cause of hyperphagia and obesity in BBS[1,5]

IMCIVREE delivered early, significant, and sustained reductions in measures of weight and hunger in BBS[1,5]

- **~8%** mean reduction in BMI in patients ≥6 years of age after 1 year[1]
  - Patients were not required to change their diet or exercise routine[5]
- Clinically significant **-0.8** mean change in BMI Z-score in patients <18 years of age[5]*
  - **100%** of patients <12 years of age achieved a clinically significant ≥0.2 reduction in BMI Z-score (n=3)[5,6]
- Clinically significant **~10%** mean weight reduction in patients ≥18 years of age[5]
- Statistically significant reduction in maximal hunger score[1†]

Well-established safety and tolerability profile

- The most common adverse reactions in IMCIVREE-treated patients were hyperpigmentation disorders, injection site reactions, and nausea[1]
- AEs were generally mild and transient[5]
- No serious AEs related to IMCIVREE were reported in the BBS trial[5]

Rhythm InTune provides your patients with personalized support

- For more information about Rhythm InTune or to request support, contact us at:

patientsupport@rhythmtx.com 1-855-206-0815

Download and complete the IMCIVREE Start Form to start a patient on IMCIVREE

*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%.[6]

†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]

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 on page 13 and full Prescribing Information.

Rhythm® PHARMACEUTICALS

IMCIVREE® (setmelanotide) injection