

Rhythm Pharmaceuticals

IMCIVREE (Setmelanotide) FDA Approval in Acquired Hypothalamic Obesity

March 19, 2026

Rhythm[®]
PHARMACEUTICALS



On Today's Call

- David Connolly, Vice President of Investor Relations and Corporate Communications
- David Meeker, MD, Chair, President and Chief Executive Officer
- Jennifer Lee, Executive Vice President, Head of North America
- Hunter Smith, Chief Financial Officer
- Alicia Fiscus, Senior Vice President, Head of Global Regulatory Affairs

Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the safety, efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication; the approval and use of IMCIVREE in patients with acquired hypothalamic obesity and its availability for patients; the commercial growth of IMCIVREE; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates, including the Type II variation request to the European Medicines Agency and the anticipated decision by the Committee for Medicinal Products for Human Use to issue an opinion to the European Commission and a potential marketing authorization in the second half of 2026; as well as the Company's engagement with Japan's Pharmaceuticals and Medical Devices Agency and plans to seek authorization for setmelanotide to treat acquired hypothalamic obesity in Japan; the estimated market size and addressable population for our drug products, including IMCIVREE for the treatment of hypothalamic obesity in the United States, the European Union and Japan; the future announcement of data from our ongoing clinical trials, including the Japanese cohort of our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity, the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity; Part C of the Phase 1 trial evaluating RM-718, and the open-label Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome; the ongoing enrollment in and potential progress or outcomes of our clinical trials; the presentation of the full data from the TRANSCEND study at an upcoming medical meeting; and the content, date and timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, our ability to successfully commercialize setmelanotide, our liquidity and expenses, our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel, and general economic conditions, and the other important factors, including those discussed under the caption "Risk Factors" in Rhythm's Annual Report on Form 10-K for the year ended December 31, 2025 and our other filings with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation and the accompanying oral presentation, whether as a result of new information, future developments or otherwise.

David Meeker, MD

Chair, President and CEO



IMCIVREE[®]
(setmelanotide) injection

NOW APPROVED

**for acquired hypothalamic obesity in
people 4 years and older**

IMCIVREE: First and Only Therapy Approved for Acquired HO

INDICATIONS AND USAGE

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated to reduce excess body weight and maintain reduction long term in adults and pediatric patients aged:

- 4 years and older with acquired hypothalamic obesity (HO).
- 2 years and older with Bardet-Biedl syndrome (BBS).
- 2 years and older with pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

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:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign.
- Other types of obesity not related to acquired HO, BBS, or POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.



Highlights of U.S. Prescribing Information

DOSAGE AND ADMINISTRATION

Recommended starting dosage injected subcutaneously for Adults and Pediatric patients aged 6 years and older with Acquired HO:

- 0.5 mg (0.05 mL) once daily for 2 weeks.
- 1 mg (0.1 mL) once daily for weeks 3-4.
- 2 mg (0.2 mL) once daily for weeks 5-6.
- 3 mg (0.3 mL) once daily for weeks 7 and onward.

ADVERSE REACTIONS

- Most common adverse reactions (incidence $\geq 20\%$ in at least 1 indication) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

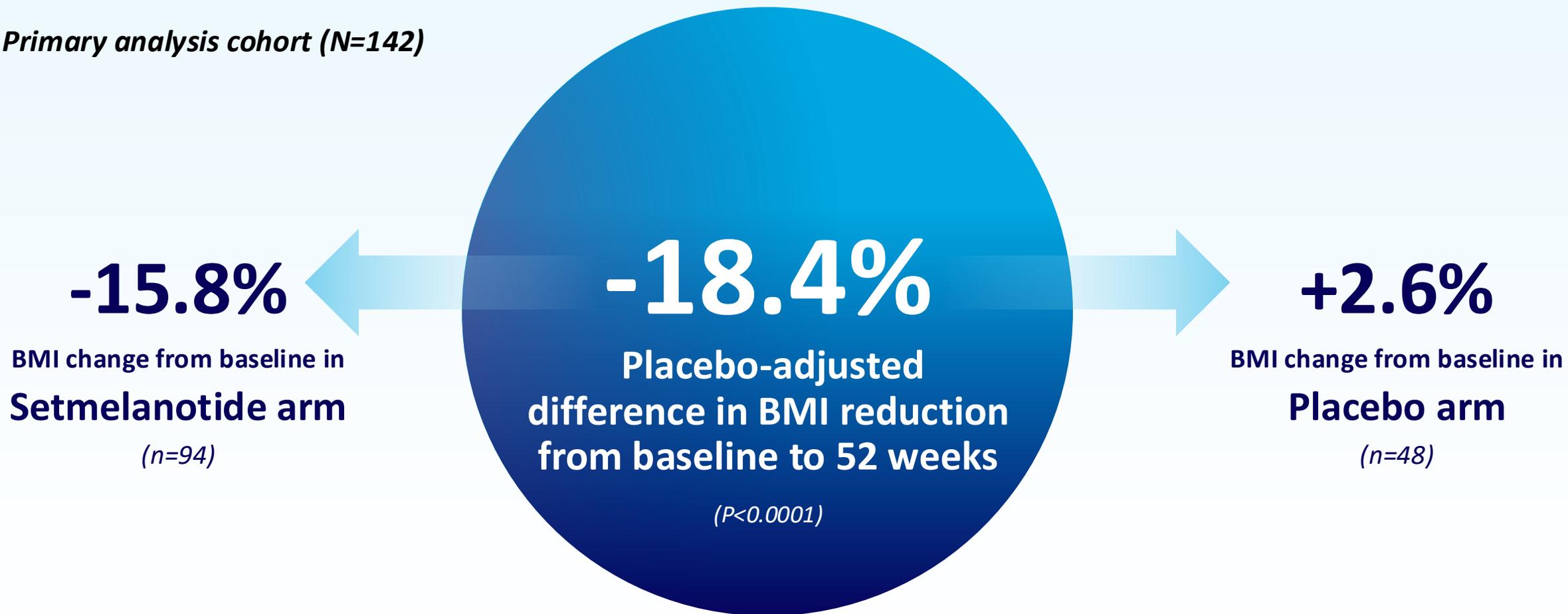
WARNING AND PRECAUTIONS

- Disturbance in Sexual Arousal
- Depression and Suicidal Ideation
- Hypersensitivity Reactions
- Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi
- Acute Adrenal Insufficiency in Patients with Acquired HO: Monitor patients for signs of acute adrenal insufficiency
- Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus



Approval Supported By Statistically Significant and Highly Clinically Meaningful BMI Reduction in Phase 3 Acquired HO Trial

Primary analysis cohort (N=142)



NOTE: Shown are the least square (LS) means for setmelanotide and placebo groups and the LS mean difference in mean percentage change from baseline in BMI at Week 52, obtained from an analysis of covariance (ANCOVA) model. Rubin's Rule was used to provide the overall estimates of differences in LS means and p-value.

Advancing MC4R Agonism in Acquired Hypothalamic Obesity

U.S. FDA approval for
Acquired Hypothalamic
Obesity



2022



- Achieved proof of concept (POC) in setmelanotide Phase 2 trial

2023



- Initiated global Phase 3 TRANSCEND trial

2024

2025



- Positive Phase 3 TRANSCEND trial results
- Achieved POC with bivamelagon (daily oral)
- Initiated RM-718 (weekly injectable) Phase 1, Part C trial

2026

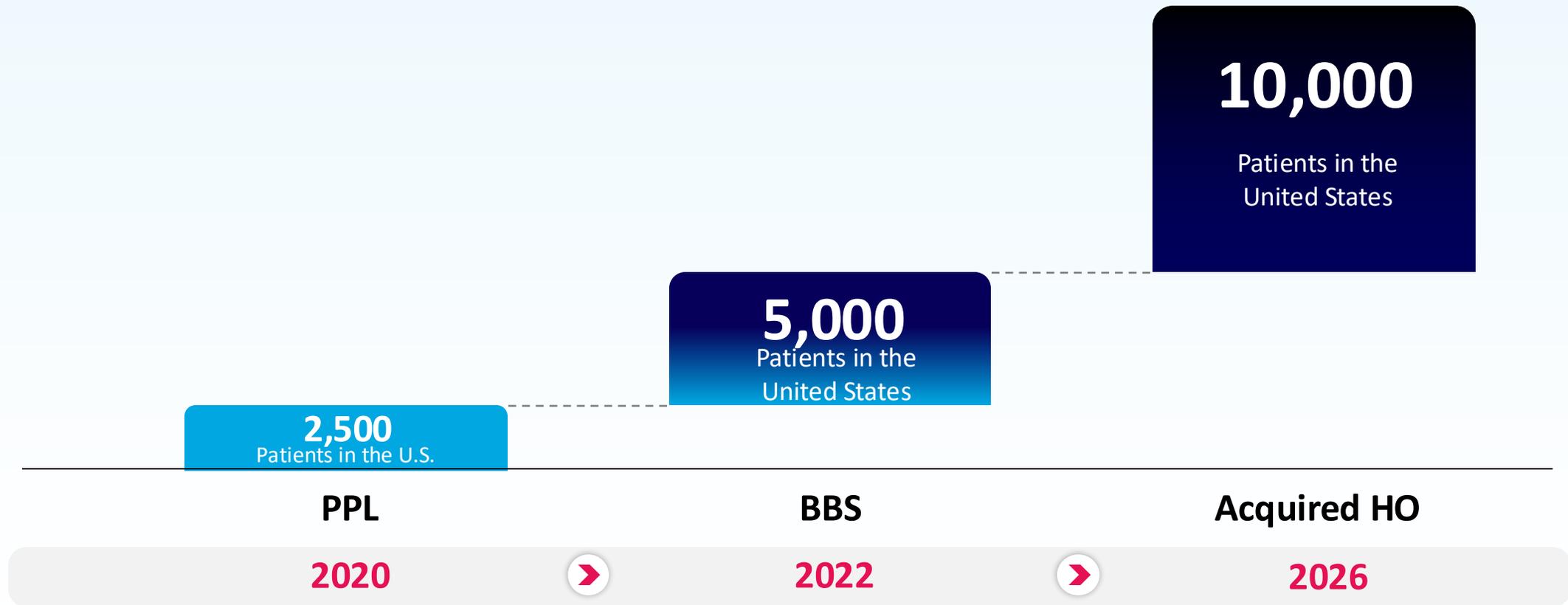


- EMA regulatory review ongoing; CHMP opinion expected in Q2
- Anticipated update on topline data from Japanese cohort in Phase 3 trial and Japan regulatory submission

Jennifer Lee

EVP, Head of North America

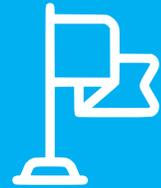
Label Expansion Expands the Reach of IMCIVREE in the U.S.



NOTE: Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates

Experienced Rare Disease Team in Place to Support Launch

**Territory
managers
in the field**



**Access team
supporting
reimbursement**



Rhythm
InTune
Support made personal

Diagnostic Journey: Meeting the Patients Where They Are

1

Patient Treated for Brain Tumor

- All patients are educated on aHO as a possible repercussion



2

Patient Develops Acquired HO

- All incident patients are accurately diagnosed within first year of onset
- Prevalent patients are expedited in their diagnosis



3

Patient's Obesity is Addressed

- All appropriate patients are treated with IMCIVREE
- Support patients on therapy



Setmelanotide Product Profile Resonates with Endocrinologists

In a hypothetical placebo-controlled trial, how compelling would you find
15% BMI reduction vs 0% for placebo?

94% extremely compelling
or compelling

100% would prescribe
setmelanotide to
patients with HO

(N=50)



I love seeing that there is improvement in a patient-centered outcome – that being the change in hunger. For me, it's not all weight-centric all the time – I think we get really focused on that"

- Endocrinologist

Transformative Day for HO Community



Patients waiting
for a therapy



First and only
approved therapy



Ready to
launch

IMCIVREE™
(setmelanotide) injection

Questions