Rhythm Pharmaceuticals Announces Presentation of Four Datasets at ObesityWeek® 2025

November 10, 2025

– Phase 3 TRANSCEND trial data showed setmelanotide achieved significant BMI reductions in patients with acquired hypothalamic obesity on concomitant treatment with GLP-1 therapy –

– Analysis of data from Phase 3 TRANSCEND trial show clinically meaningful changes in cardiometabolic parameters in patients with acquired hypothalamic obesity treated with setmelanotide for 52 weeks –

BOSTON, Nov. 10, 2025 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients living with rare neuroendocrine diseases, today announced that Rhythm and its partners delivered four Rhythm data presentations at ObesityWeek® 2025, held last week in Atlanta, GA.

“Acquired hypothalamic obesity is a severe and complex disease that profoundly impacts the lives of patients and families, affecting not only body weight and hunger, but also causing severe implications for daily functioning,” said Christian Roth, M.D., Seattle Children’s Research Institute. “Multiple presentations at ObesityWeek showed that setmelanotide delivers robust reductions in BMI whereas previous studies testing anti-obesity medicines for the treatment of acquired hypothalamic obesity did not result in consistent sustained weight loss. Importantly, setmelanotide resulted in meaningful improvements in cardiometabolic health and patient-reported outcomes, highlighting its potential to transform the lives of patients living with acquired hypothalamic obesity.”

Dr. Roth delivered an oral presentation detailing previously disclosed results from a post-hoc analysis of Phase 3 TRANSCEND data of setmelanotide in patients with acquired hypothalamic obesity who received concomitant GLP-1 therapy during the trial. Highlights from the presentation include:

- -27.1% ($p<0.0001$) mean placebo-adjusted difference in BMI reduction in patients (n=9) treated with setmelanotide and GLP-1 therapy concurrently compared with GLP-1 therapy and placebo (n=6); and
- -19.0% ($p<0.0001$) mean placebo-adjusted difference in BMI reduction in patients treated with setmelanotide (n=72) compared with placebo (n=33); none of these patients were on GLP-1 therapy during the trial.

Dr. Roth also presented a poster titled, “Patient- and Caregiver-Reported Experience with Acquired Hypothalamic Obesity in the TRANSCEND Trial.” The results from interviews with 14 trial participants and 16 caregivers of trial participants younger than 12 showed that patients consistently reported meaningful and beneficial changes in hunger, weight, energy levels, and physical activity with setmelanotide therapy.

Cardiometabolic Results From a Phase 3 Trial of Setmelanotide in Acquired Hypothalamic Obesity
Jennifer Miller, M.D., University of Florida Division of Endocrinology, Department of Pediatrics in the College of Medicine, was the lead author on a poster that showed setmelanotide treatment was associated with significant improvement across most cardiometabolic parameters and proteomic biomarkers. Results showed improvements across nonambulatory blood pressure, lipid levels, and hematologic and chemistry parameters.

Hyperphagia and the Identification of Genetic Variants in Patients With Early-Onset Obesity
Roohi Kharofa, M.D., Cincinnati Children’s Hospital Medical Center, presented a poster on hyperphagia and the identification of genetic variants in patients with early-onset obesity. This prospective observational study collected data from 212 participants from three Pediatric Obesity Weight Evaluation Registry (POWER) sites.

All of the Rhythm-related presentations from TOS 2025 are available here: https://hcp.rhythmtx.com/publications-presentations/.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with rare neuroendocrine diseases. Rhythm’s lead asset, IMCIVREE® (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity, is approved by the U.S. Food and Drug Administration (FDA) to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency. Both the European Commission (EC) and the

UK's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare diseases, as well as investigational MC4R agonists bivamelagon and RM-718, and a preclinical suite of small molecules for the treatment of congenital hyperinsulinism. Rhythm's headquarters is in Boston, MA.

Setmelanotide Indication
In the United States, setmelanotide is indicated to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS), POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the European Union and the United Kingdom, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above. In Europe, setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide 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 POMC, PCSK1 or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity.

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

WARNINGS AND PRECAUTIONS

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred because of its pharmacologic effect. Full body skin examinations prior to initiation and periodically during treatment should be conducted to monitor pre-existing and new pigmentary lesions.

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.

Pediatric Population: The prescribing physician should periodically assess response to setmelanotide therapy. In growing children, the impact of weight loss on growth and maturation should be evaluated. In Europe, the prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

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 +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See section 4.8 of the Summary of Product Characteristics for information on reporting

suspected adverse reactions in Europe.

Please see the full U.S. Prescribing Information and EU Summary of Product Characteristics for additional Important Safety Information.

Forward-looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of setmelanotide and other product candidates, the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage, including the potential benefits of setmelanotide for patients with BBS or POMC, PCSK1, or LEPR deficiency; expectations surrounding pending and potential regulatory submissions and approvals, including within the United States, the EU and other regions; business strategy and plans, including regarding commercialization of setmelanotide in the United States, the EU and other regions; and the 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, 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 discussed under the caption "Risk Factors" in Rhythm's Quarterly Report on Form 10-Q for the three months ended September 30, 2025 and 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 release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

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