Rhythm Pharmaceuticals Announces Preliminary Data from Exploratory Phase 2 Trial that showed Setmelanotide Demonstrated Positive Efficacy Signal in Prader-Willi Syndrome

December 11, 2025

-- BMI and hyperphagia reductions have been observed in patients with PWS treated with setmelanotide at Month 3 (n=8) and Month 6 (n=5); 17 of 18 enrolled patients remain on therapy --

-- Promising results supportive of Phase 3, registrational trial of setmelanotide in PWS --

-- Company initiated Phase 1, Part D study to evaluate weekly MC4R agonist RM-718 in patients with PWS --

-- Company to hold conference call on Thursday, December 11 at 8:00 a.m. --

BOSTON, Dec. 11, 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 positive preliminary results from its exploratory Phase 2 trial of setmelanotide in patients with Prader-Willi syndrome (PWS).

The Company also announced plans to advance setmelanotide into a Phase 3 registrational trial in PWS, pending successful completion of this Phase 2 trial. Rhythm also announced that it has initiated a Part D arm in the Phase 1 trial of MC4R agonist RM-718 that will enroll up to 20 patients with PWS. Rhythm anticipates screening the first patient for this 26-week open-label trial of RM-718 in December 2025.

“There remains a profound unmet need in the PWS patient population,” said Jennifer Miller, M.D., University of Florida Division of Endocrinology, Department of Pediatrics in the College of Medicine, the principal investigator for this Phase 2 trial. “Hyperphagia and severe obesity associated with PWS present serious challenges for patients and often lead to significant health complications over time. These interim data offer meaningful insight into the potential for a future treatment option that could help address the unique and critical needs of patients living with PWS.”

Rhythm enrolled 18 patients with PWS aged 6-65 years old with a BMI ≥30 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and sex for patients younger than 18. The 52-week trial remains ongoing.

Setmelanotide therapy demonstrated potential therapeutic benefit with BMI and hyperphagia reductions in patients with PWS at Month 3 (n=8) and Month 6 (n=5); Highlights from preliminary results, as of a cut-off date of Nov. 14, include:

- Six (6) of 8 patients who reached Month 3 of setmelanotide therapy achieved BMI reductions from baseline;
- Three (3) of 5 patients who reached Month 6 of setmelanotide therapy achieved reductions in BMI, with two seeing deeper reductions versus Month 3 and one unchanged;
- Six (6) of 7 evaluable patients who reached Month 3 of setmelanotide therapy achieved meaningful reduction in Hyperphagia Questionnaire for Clinical Trials[1] (HQ-CT) scores; one patient’s baseline and Month 3 HQ-CT score was 0, therefore not evaluable;
- Seventeen (17) of the 18 patients enrolled remain on active setmelanotide therapy; and
- Safety and tolerability results have been consistent with setmelanotide’s well-established clinical profile.

“We are encouraged by these preliminary results, which give us confidence to advance setmelanotide into a registrational Phase 3 trial for PWS,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “We look forward to additional data in the first half of 2026 and remain committed to exploring the potential of MC4R agonism for this patient population, for whom there are very few treatment options available. In parallel, we look forward to evaluating our weekly MC4R agonist RM-718 in PWS, and we expect the first patient with PWS to enter screening for this study in December.”

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8:00 a.m. ET on Thursday, December 11 to discuss this update. Participants may register for the conference call here. It is recommended that participants join the call ten minutes prior to the scheduled start.

A webcast of the call will also be available under "Events and Presentations" in the Investor Relations section of the Rhythm Pharmaceuticals website at https://ir.rhythmtx.com/. The archived webcast will be available on Rhythm Pharmaceuticals' website approximately two hours after the conference call and will be available for 30 days following the call.

About the Phase 2 PWS Trial

This trial is a single-site, open-label Phase 2 study evaluating setmelanotide for the treatment of PWS. Originally designed as a 26-week trial, the duration was extended to 52 weeks to allow early participants to remain on therapy.

Eighteen patients with PWS and obesity, aged 6 to 65 years, were enrolled. Participants were dose-escalated to 5 mg/day of setmelanotide, as tolerated. The primary endpoints are safety and tolerability, with key secondary endpoints assessing weight, hyperphagia, behavior, and pharmacokinetics. Safety and tolerability findings to date have been consistent with setmelanotide's established profile.

About Prader-Willi Syndrome
PWS is a rare genetic disorder that results in a number of physical, mental and behavioral problems. A key feature of PWS is a constant sense of hunger that usually begins at about 2 years of age. PWS is estimated to affect approximately 400,000 people worldwide and approximately 20,000 people in the United States. There are currently limited therapeutic options that effectively reduce the extreme hyperphagia and address low resting energy expenditure associated with PWS.

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 of setmelanotide, RM-718 and other product candidates; clinical design, enrollment, or progress, and preliminary, interim and final data readouts; potential regulatory submissions, approvals and timing thereof of setmelanotide, RM-718 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 or RM-718 for patients with PWS, 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; our participation in upcoming events and presentations; 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.

Corporate Contact:
David Connolly
Head of Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

Media Contact:
Layne Litsinger
Real Chemistry

llitsinger@realchemistry.com

[1] The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a 9-item, observer-reported outcome measure that assesses changes in hyperphagic behaviors in individuals with PWS. Each item is scored from 0 to 4, for a total possible score of 36.

Source: Rhythm Pharmaceuticals, Inc.