Rhythm Pharmaceuticals Presents Positive Interim Six-month Data from Phase 2 Trial of Setmelanotide in Patients with Prader-Willi Syndrome (PWS) at ENDO 2026

June 13, 2026

-- Patients with PWS treated with setmelanotide therapy (N=17) achieved clinically meaningful BMI or BMI z-score reductions, reductions in fat mass with preservation of lean mass, and improvements in hyperphagia and anxiety measures --

-- Positive results reinforce rationale for Phase 3 development of MC4R agonism in PWS --

-- Company to hold conference call on Saturday, June 13, at 8 a.m. CT, 9 a.m. ET --

BOSTON, June 13, 2026 (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 preliminary data from a Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome (PWS) delivered during the Endocrine Society's Annual Meeting (ENDO 2026) in Chicago.

"Patients and families living with PWS face severe hyperphagia and obesity due to underlying MC4R pathway dysfunction and have limited effective treatment options. These results show that MC4R agonism has the potential to deliver sustained and durable improvements in outcomes across BMI, hyperphagia scores, body composition, and food-related behaviors and anxiety," 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. "Importantly, such reductions in HQ-CT score and anxiety, as well as weight reduction, have the potential to ease the burden not only on patients, but also on their caregivers who manage the daily challenges of this disease."

Rhythm enrolled 18 patients with PWS aged 6-23 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 in this Phase 2 trial. The 52-week trial remains ongoing, and 17 patients remain on active therapy as of June 12, 2026.

Results from the six-month analysis demonstrate that treatment with setmelanotide was associated with improvements across multiple clinically relevant endpoints, as of a data cut off date of May 7, 2026. Highlights include:

- Consistent BMI reductions in pediatric and adult patients at Month 6:
  - -3.06% mean reduction in BMI (N=17 pts);
  - -3.11% mean reduction in BMI in adult patients (n=10); with six achieving >2.5% BMI reduction, and four achieving >4% BMI reduction;
  - −3.00% mean reduction in BMI in pediatric patients (n=7);
  - −0.35 mean reduction in BMI z-score from baseline in pediatric patients (n=7);
  - Five (5) of seven pediatric patients achieved clinically meaningful BMI z-score reduction ≥0.2;
- Setmelanotide achieved preservation of lean mass and reductions in fat mass across 16 patients with data available from DEXA scans:
  - +0.74% mean gain in lean mass and -4.19% mean loss in fat mass across 16 patients;
  - Six (6) of nine adult patients achieved >5% reduction in fat mass;
  - Five (5) of seven pediatric patients gained ≥2.95% in lean mass;
- Clinically meaningful improvement in hyperphagia score observed in patients with moderate to severe hyperphagia, defined as a ≥7-point reduction in Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score
  - Eight (8) of 10 patients who entered trial with moderate to severe hyperphagia (≥13 at baseline) achieved clinically meaningful improvement of 7 points or better.
- Improvement in PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) which measures anxiousness, emotional distress, and behavioral dysregulation.
  - Of the 15 patients who had a baseline score >11, 10 patients achieved clinically meaningful improvement of ≥11 points; and
- Safety and tolerability results have been consistent with the well-established profile observed with setmelanotide.

"These results demonstrate the potential for MC4R agonists to address the underlying biology of this severe disease and

increased our confidence to advance into Phase 3 trials for PWS," said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm.

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. Rhythm estimates there are between 12,500 and 16,000 patients living with PWS in the United States and a similar number in Europe, based on updated internal prevalence estimates developed using a bottoms-up methodology analyzing incidence, age-specific survival and claims-based validation. Further, the Company estimates that 80% to 90% of PWS patients are living with hyperphagia and obesity, or approximately 8,500 – 12,750 patients. There are currently limited therapeutic options that effectively reduce the extreme hyperphagia and address low resting energy expenditure associated with PWS.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8 a.m. CT/ 9 a.m. ET on Saturday, June 13, to discuss these data. 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.

Multiple Rhythm presentations from ENDO 2026 will be available in the afternoon on Monday, June 15, at: 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 aged 4 years and older with acquired hypothalamic obesity, 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. The European Commission (EC) has authorized setmelanotide for the treatment of obesity and control of hunger in patients 4 years of age and above with acquired hypothalamic obesity; and both the 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 adults and pediatric patients aged 4 years and older with acquired hypothalamic obesity, in adult and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or 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).

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 the European Union and the United Kingdom, 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 acquired HO, BBS, or POMC, PCSK1 or LEPR deficiency, 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 and increased frequency of penile erections in males 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.

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 occurred in the majority of IMCIVREE-treated patients. IMCIVREE may also cause development of new melanocytic nevi or darkening of pre-existing nevi. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmented lesions.

Acute Adrenal Insufficiency with Acquired HO: Patients with acquired HO and secondary adrenal insufficiency reported serious adverse reactions related to acute adrenal insufficiency in 5% of IMCIVREE-treated patients and no placebo-treated patients. In patients with secondary adrenal insufficiency, monitor for clinical signs of acute adrenal insufficiency.

Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus: Patients with acquired HO and concomitant central diabetes insipidus (DI)/arginine vasopressin (AVP) deficiency reported hyponatremia in 6% of IMCIVREE-treated patients and 2% of placebo-treated patients and hypernatremia in 5% of IMCIVREE-treated patients and 4% of placebo-treated patients. Monitor serum sodium levels with changes in fluid intake and hydration status. Adjust the doses of concomitant therapies for DI/AVP deficiency as needed.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20% in at least 1 indication) 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 http://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 Prescribing Information 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 safety, efficacy, potential benefits of, and clinical design or progress, potential regulatory submissions, approvals and timing thereof for any of our products or product candidates at any dosage or in any indication; the presentation of clinical data and results from our trials, including the ongoing Phase 2 trial of setmelanotide in patients with PWS, clinical and real-world efficacy and safety data related to the use of setmelanotide and bivamelagon in patients with acquired hypothalamic obesity BBS and our participation in upcoming events and presentations, including at ENDO 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 other important factors, including those discussed under the caption “Risk Factors” in Rhythm’s Quarterly Report on Form 10-Q for the three months ended March 31, 2026, 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 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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