Rhythm Pharmaceuticals Announces Additional Positive Data from Phase 3 TRANSCEND trial of Setmelanotide in Patients with Acquired Hypothalamic Obesity

March 1, 2026

-- -18.8% placebo-adjusted difference in BMI reduction achieved in all patients (N=142) at 52 weeks, including 12 Japanese patients and 10 supplemental patients with acquired hypothalamic obesity --

-- March 20, 2026 PDUFA goal date for sNDA for setmelanotide in acquired hypothalamic obesity --

BOSTON, March 01, 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 additional positive data from its global Phase 3 TRANSCEND trial of setmelanotide in patients with acquired hypothalamic obesity (HO). This new data set includes 12 patients from a Japanese cohort and 10 supplemental patients who were enrolled in addition to the primary 120-patient pivotal cohort.

Highlights from these 52-week data include:

- -18.8% placebo-adjusted difference[1] in BMI reduction (N=142);
- Primary endpoint of mean BMI reduction of -16.4% from baseline for all patients on setmelanotide therapy (n=94) compared with +2.4% BMI change for patients on placebo (n=48) at 52 weeks (95% CI; p<0.0001); and
- Among patients aged 12 and older (n=98), the setmelanotide group (n=66) showed an average weekly reduction of 2.5 points in the weekly average most hunger score, compared with a 1.3-point reduction in the placebo group (n=32) (p=0.0015).

“Building off our strong pivotal data, these efficacy data further support setmelanotide’s potential to become the first therapy approved for patients living with the hunger, reduced energy expenditure, accelerated weight gain, and obesity of acquired hypothalamic obesity,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “We look forward to continuing our positive dialogue with regulators, and we are well prepared to bring setmelanotide to patients with acquired HO, pending U.S. Food and Drug Administration (FDA) approval."

Rhythm previously announced the TRANSCEND trial met its primary and key secondary endpoints when it disclosed topline data from the pre-specified 120-patient pivotal cohort in April 2025. The Company’s supplemental New Drug Application (sNDA) is under review by the U.S. Food and Drug Administration (FDA) with a PDUFA goal date of March 20, 2026. Rhythm will submit the final data package to the FDA on March 2, 2026 ahead of the previously agreed upon submission date for the supplemental data.

The European Medicines Agency (EMA) is reviewing Rhythm’s Type II variation submission to the Marketing Authorization Application (MAA) for setmelanotide for the same indication. The Company anticipates the Committee for Medicinal Products for Human Use (CHMP) would issue an opinion to the European Commission (EC) in the second quarter of 2026 with potential marketing authorization in the second half of 2026. The Company will also submit the full data package to Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) and plans to seek marketing authorization for setmelanotide to treat acquired hypothalamic obesity there, as well.

About Acquired Hypothalamic Obesity
Acquired hypothalamic obesity is a rare disease characterized by accelerated and sustained weight gain caused by an injury to the hypothalamus. Hypothalamic injury may lead to decreased alpha-melanocyte-stimulating hormone (α-MSH) production and impairment of MC4R pathway signaling. The MC4R pathway is responsible for regulating energy balance and body weight. Acquired hypothalamic obesity most frequently follows the growth or treatment of craniopharyngioma, astrocytoma or other hypothalamic-pituitary tumors. Additional causes of injury may include traumatic brain injury, stroke or inflammation. Due to impairment of the MC4R pathway, patients experience accelerated and sustained weight gain, often accompanied by hyperphagia and/or decreased energy expenditure. Acquired hypothalamic obesity can occur as early as six months following hypothalamic injury. Rhythm estimates 10,000 patients living with acquired HO in the United States, approximately 10,000 patients in Europe and between 5,000 to 8,000 people living with acquired hypothalamic obesity in Japan.

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 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 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 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 <u>not</u> 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 BBS or POMC, PCSK1, or LEPR deficiency, 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

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.

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmented 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 +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 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 our pivotal Phase 3 TRANSCEND study evaluating setmelanotide for the treatment of acquired hypothalamic obesity, including the additional data set of 12 patients from a Japanese cohort and 10 supplemental patients enrolled in addition to the primary 120-patient pivotal cohort; the potential for setmelanotide to treat hypothalamic obesity; 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; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates, including the sNDA to the FDA and the PDUFA goal date of March 20, 2026, including the submission of the final data package to the FDA, the Type II variation request to the EMA and the anticipated decision by the CHMP to issue an opinion to EC and potential marketing authorization in the second half of 2026; as well as the Company's engagement with PMDA 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 setmelanotide for the treatment of hypothalamic obesity in the United States, the EU and Japan; and presentation of the full data from the TRANSCEND study at an upcoming medical meeting; including 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, uncertainties and 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 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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[1] ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. Rubin's Rule was used to provide the overall estimates of differences in least square (LS) means, corresponding CI and p-value.

Source: Rhythm Pharmaceuticals, Inc.