Rhythm Pharmaceuticals Announces The New England Journal of Medicine Publication of Phase 3 TRANSCEND Trial Results in Acquired Hypothalamic Obesity

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BOSTON, July 08, 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 that results from its pivotal Phase 3 TRANSCEND trial evaluating setmelanotide, a melanocortin-4 receptor (MC4R) agonist, in patients with acquired hypothalamic obesity have been published in *The New England Journal of Medicine* (NEJM).

The TRANSCEND study is the largest and longest placebo-controlled clinical trial ever conducted in patients with acquired hypothalamic obesity. The publication highlights robust improvements in weight and hunger achieved with setmelanotide therapy in adult and pediatric patients aged four years and older.

“Patients with acquired hypothalamic obesity and their families face an urgent need for effective treatment options,” said Dr. Christian Roth, a pediatric endocrinologist and principal investigator of the Norcliffe Foundation Center for Integrative Brain Research at Seattle Children’s Research Institute, who served as the senior author and was instrumental in the trial’s planning. “The results of the TRANSCEND trial demonstrate meaningful and consistent reductions in body mass index as well as improvements in hunger. For patients and families who experience the accelerated and sustained weight gain associated with hypothalamic injury, these findings represent a potentially transformative therapeutic advancement.”

In this 52-week, randomized, double blind, placebo-controlled Phase 3 study, the first 120 patients who reached 52 weeks on therapeutic regimen were evaluated as the primary analysis cohort. Patients treated with setmelanotide achieved:

- -19.8% placebo-adjusted difference in body mass index (BMI) reduction (n=120);
- Primary endpoint of mean BMI reduction of -16.5% from baseline for all patients on setmelanotide therapy (n=81) compared with +3.3% BMI change for patients on placebo (n=39) at 52 weeks ($p<0.0001$);
- 80% of patients on setmelanotide achieved BMI reduction of 5% or greater at 52 weeks; and
- Clinically meaningful improvements in hunger.

Setmelanotide was generally well tolerated. No new safety signals were observed, and adverse events leading to treatment discontinuation were comparable between treatment and placebo groups.

In March 2026, the U.S. Food and Drug Administration (FDA) approved setmelanotide (IMCIVREE®) as the first and only therapy for acquired hypothalamic obesity in adults and children aged 4 years and older. Also in March 2026, the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended marketing authorization for IMCIVREE to include the treatment of obesity and the control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity due to hypothalamic injury or impairment.

“Publication of the TRANSCEND data in NEJM underscores both the strength of the clinical evidence and the potential positive impact of setmelanotide for people living with acquired hypothalamic obesity,” said David Meeker, M.D., Chairman, President and Chief Executive Officer of Rhythm Pharmaceuticals. “We are deeply grateful to the study authors, investigators, patients and families whose commitment made this landmark trial possible. With FDA and EU approvals now in place and the regulatory submission under review in Japan, our goal is to bring this first-in-class therapy to patients worldwide who urgently need a targeted treatment option.”

About the Phase 3 TRANSCEND Trial
The global, randomized, double blind, placebo-controlled Phase 3 TRANSCEND trial evaluated the efficacy and safety of setmelanotide in patients aged 4 years and older with acquired hypothalamic obesity. A total of 120 participants were randomized 2:1 to once daily subcutaneous setmelanotide or placebo for 52 weeks. The primary endpoint was mean percent change in BMI after 52 weeks of treatment. Full topline results were previously announced in April 2025.

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.

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 any of our other product candidates in patients with acquired hypothalamic obesity and our participation in upcoming events and presentations and publications, including the publication of the results from our pivotal Phase 3 TRANSCEND trial evaluating setmelanotide in patients with acquired hypothalamic obesity in The New England Journal of Medicine, 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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