Rhythm Pharmaceuticals Announces Publication of Results from Phase 2 Study of Setmelanotide for the Treatment of Hypothalamic Obesity in The Lancet Diabetes & Endocrinology

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- Publication highlights administration of setmelanotide therapy resulted in a mean percent reduction in BMI of 15% at 16 weeks and 26% at one year of treatment -

- Topline data from ongoing pivotal Phase 3 clinical trial in hypothalamic obesity on track for 2Q 2025 -

BOSTON, April 29, 2024 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with rare neuroendocrine diseases, today announced the publication of previously disclosed results from its Phase 2 study of setmelanotide for the treatment of hypothalamic obesity. The data are published in the peer-reviewed journal The Lancet Diabetes & Endocrinology.

"People with hypothalamic obesity experience rapid, severe weight gain and hyperphagia," said lead author Christian Roth, M.D., Seattle Children's Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington. "In this first study to investigate the use of setmelanotide as a targeted treatment for hypothalamic obesity, we observed a consistent reduction in body weight and hunger in all adherent patients. We believe these findings support setmelanotide as a potential novel and effective treatment option, and we look forward to potentially confirming the results in the ongoing pivotal study."

Acquired hypothalamic obesity is a rare form of extreme obesity that occurs following damage to the hypothalamic region of the brain, which includes the melanocortin-4 receptor (MC4R) pathway and is responsible for controlling physiological functions such as hunger and weight regulation. It most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma, or other rare brain tumors. Patients experience rapid weight gain, a reduction in energy expenditure, and an increase in hunger leading to severe obesity within six to 12 months following tumor resection.

Rhythm enrolled 18 patients in its open-label, 16-week Phase 2 trial designed to evaluate setmelanotide in acquired hypothalamic obesity in patients with a body mass index (BMI) ≥95th percentile (children 6 to <18 years) or ≥35 kg/m^2 (adults ≥18 years). The primary endpoint was the proportion of patients who achieved a 5% or greater reduction in BMI after 16 weeks of treatment. Hunger was also assessed daily, as self-reported by individual patients. As previously disclosed, results demonstrated:

- 89% (16 of 18) of patients achieved the primary endpoint;
- 78% (14 of 18) of patients achieved a 10% or greater reduction in BMI at 16 weeks;
- Mean percent reduction in BMI was 15% from baseline;
- In pediatric patients (n=13), the mean (standard deviation [SD]) BMI Z score at Week 16 was 2.7 (1.3), a reduction of 1.3 (1.0) points from baseline; and
- Mean (SD) most hunger score at baseline was 6.6 (1.6), compared with 3.7 (2.5) at Week 16, for a reduction of –2.9 (2.3) points or 45% for patients ≥12 years of age (n=11).

The publication also includes preliminary data from Rhythm's long-term extension of the Phase 2 study that were disclosed at ObesityWeek® 2023. These data show patients with hypothalamic obesity (n=12) achieved mean BMI reduction of approximately 26% at one year on setmelanotide treatment.

Consistent with prior experience, setmelanotide was generally well tolerated. The most common adverse events (AEs) in the primary trial included nausea (61.1%), vomiting (33.3%), skin hyperpigmentation (33.3%), diarrhea (22.2%), and COVID-19 (22.2%). Two patients discontinued due to AEs and a third patient was non-compliant. There were no serious AEs, no AEs that led to study discontinuation during the trial, and no new safety concerns were observed during the long-term extension trial.

In January 2024, Rhythm announced the completion of screening for enrollment in the ongoing pivotal, Phase 3 clinical trial evaluating setmelanotide in patients with acquired hypothalamic obesity. The Company remains on track to obtain topline study results in the first half of 2025.

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) for chronic weight management in

adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). 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 6 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 LB54640 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 for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to 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) or BBS.

In the European Union, 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 6 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 Pigmentation and Darkening of Pre-Existing 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.

Heart rate and blood pressure monitoring: In Europe, heart rate and blood pressure should be monitored as part of standard clinical practice at each medical visit (at least every 6 months) for patients treated with setmelanotide.

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Patients who have an erection lasting longer than 4 hours should seek emergency medical attention.

Depression and Suicidal Ideation: Depression and suicidal ideation have occurred. Patients should be monitored for new onset or worsening depression or suicidal thoughts or behaviors. Consideration should be given to discontinuing setmelanotide 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 setmelanotide.

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: Setmelanotide 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

Lactation: Not recommended when breastfeeding.

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 the potential, safety, efficacy, regulatory progress, clinical design or progress, and commercial market for any of our products or product candidates, including setmelanotide to treat hypothalamic obesity; and the ongoing progress of and anticipated timing for our Phase 3 clinical trial. Statements using word 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, whether the conditions for the closing of the investment transaction; 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 our Annual Report on Form 10-K for the year ended December 31, 2023 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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