Rhythm Pharmaceuticals Presents Data on MC4R Agonists Setmelanotide and Bivamelagon at ENDO 2025

July 12, 2025

- Presentations highlight clinically meaningful reductions in BMI in patients with acquired hypothalamic obesity –

- Full data from Phase 3 TRANSCEND study underscore potential efficacy of setmelanotide, including with prior use or concomitant use of GLP-1s -

BOSTON, July 12, 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 data from three new presentations on the Company's clinical programs for acquired hypothalamic obesity at the Endocrine Society's Annual Meeting (ENDO 2025) taking place July 12-15 in San Francisco, CA.

Acquired hypothalamic obesity is a rare but serious condition caused by damage to the hypothalamic region of the brain, which includes the melanocortin-4 receptor (MC4R) pathway. This damage, often from brain tumors or their treatment, leads to rapid weight gain, hyperphagia, and low energy expenditure. Presentations on Rhythm's acquired hypothalamic obesity programs at ENDO 2025 include:

Efficacy and Safety of Once-Daily Oral Bivamelagon in Acquired Hypothalamic Obesity: Results from a Double-blind, Multicenter, Placebo-Controlled, Randomized Phase 2 Trial
In a poster presentation, Vidhu Thaker, M.D., Pediatric Endocrinology, Columbia University, New York City, presented data from the Phase 2 SIGNAL trial evaluating bivamelagon, a daily oral, highly selective MC4R agonist, in patients with acquired hypothalamic obesity. In the 14-week, double-blind, four-arm, placebo-controlled portion of the trial, bivamelagon achieved statistically significant and clinically meaningful reductions in body mass index (BMI), consistent with BMI reductions achieved with setmelanotide therapy in similar patient populations in past trials. Other highlights include:

- -9.3% BMI reduction from baseline in the 600mg cohort (n=8) (p-value= 0.0004);
- -7.7% BMI reduction from baseline in the 400mg cohort (n=7) (p-value= 0.0002);
- -2.7% BMI reduction from baseline in the 200mg cohort (n=6) (p-value= 0.0180); and
- BMI for patients in the placebo cohort (n=7) increased by 2.2% over 14 weeks.

"Patients with acquired hypothalamic obesity struggle with accelerated weight gain that profoundly affects their life. These data demonstrate bivamelagon's potential as a transformative therapeutic option for patients and validate the potential opportunity for MC4R targeted therapies, if approved, to become the standard of care for this patient community," said Vidhu Thaker, M.D., Associate Professor, Pediatric Endocrinology and Molecular Genetics, Department of Pediatrics, Columbia University Irving Medical Center, New York City.

Efficacy and Safety of Setmelanotide in Acquired Hypothalamic Obesity: Results from a Double-Blind, Multicenter, Placebo-Controlled, Randomized Phase 3 Trial
In a live oral presentation, Susan Phillips, M.D., Pediatric Endocrinology, University of California San Diego/Rady Children's Hospital, San Diego, presented data from Rhythm's pivotal Phase 3 TRANSCEND trial evaluating setmelanotide, the largest randomized, placebo-controlled trial in acquired hypothalamic obesity to date. Highlights from the presentation include:

- -19.8% placebo-adjusted difference in BMI reduction (N=120);
- Statistically significant BMI reductions following setmelanotide treatment were consistently observed across subgroups stratified by age (<12, 12 to 17, <18, and 18 years and older; ranging from -15.6% to -17.2%) and by sex (-16.3% female; -16.8% male)
- Significant BMI reductions observed in participants with prior use or concomitant use of GLP-1s:
    - Mean reduction of -19.3% in BMI from baseline for participants with prior but no concomitant GLP-1 use (n=10) compared to + 5.4% change for participants on placebo (n=6) at 52 weeks (p<0.0001);
    - Mean reduction of -25.1% change in BMI from baseline for participants with prior and concomitant GLP-1 use (n=9) compared to +2.0% change for participants on placebo (n=6);
- There was significant reduction in weight-related measures in participants <18 years of age with setmelanotide at week 52, with a -26.2% change in the 95th percentile for BMI.

"The TRANSCEND trial has notably demonstrated how setmelanotide has the potential to significantly alter the trajectory of this

devastating condition and provide significant benefit to both children and adult patients. The nearly 20% placebo-adjusted difference in BMI reduction is very compelling." said Susan Phillips, M.D., pediatric endocrinologist at Rady Children's Hospital-San Diego and professor at UC San Diego School of Medicine.

Experiences and Observations with Acquired Hypothalamic Obesity: A Qualitative Interview Sub-Study
Finally, on July 14, from 12:00 PM - 1:30 PM PT, Christian Roth, M.D., Seattle Children's Research Institute, will present a poster detailing results from exit interviews gathered from 30 patients or caregivers located in the United States with acquired hypothalamic obesity who participated in the Phase 3 TRANSCEND trial.

All of the Rhythm-related presentations from ENDO 2025 will be available here: 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 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.

About Acquired Hypothalamic Obesity
Acquired hypothalamic obesity is a rare form of 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. Acquired hypothalamic obesity most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma or other rare brain tumors. Additional causes of injury may include traumatic brain injury, stroke, or inflammation due to infection. Patients experience accelerated weight gain, a reduction in energy expenditure, and hyperphagia (a chronic pathological condition characterized by insatiable hunger, impaired satiety, and persistent abnormal food-seeking behaviors) leading to severe obesity within six to 12 months following tumor resection or other injury.

Rhythm estimates there are 5,000 to 10,000 people living with hypothalamic obesity in the U.S., 5,000 to 8,000 people living with hypothalamic obesity in Japan, and 3,500 to 10,000 people living with hypothalamic obesity in the E.U.

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 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 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 Phase 2 study to assess the efficacy and safety of bivamelagon in patients with acquired hypothalamic obesity and the potential for bivamelagon to treat or become a standard of care for hypothalamic obesity; our pivotal Phase 3 TRANSCEND study evaluating setmelanotide for the treatment of acquired hypothalamic obesity and the potential for setmelanotide to treat or become a standard of care for hypothalamic obesity; the safety, efficacy, potential benefits of, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of bivamelagon, setmelanotide and other product candidates; the clinical design or progress of any of our products or product candidates at any dosage or in any indication; 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 bivamelagon and setmelanotide for patients with acquired hypothalamic obesity or congenital hypothalamic obesity; our participation in upcoming events and presentations, and the date, time and content thereof 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, 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, including those discussed under the caption "Risk Factors" in Rhythm's Quarterly Report on Form 10-Q for the three months ended March 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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Source: Rhythm Pharmaceuticals, Inc.