Rhythm Pharmaceuticals Announces Pivotal Phase 3 TRANSCEND Trial Meets Primary Endpoint with -19.8% Placebo-adjusted BMI Reduction in Patients (N=120) with Acquired Hypothalamic Obesity

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-- Patients with acquired hypothalamic obesity on setmelanotide therapy (n=81) achieved mean BMI change of -16.5% compared with +3.3% for placebo (n=39) at 52 weeks (p<0.0001) --

-- -19.2% placebo-adjusted BMI reduction achieved in adult patients 18 years old and older (n=49) at 52 weeks --

-- -20.2% placebo-adjusted BMI reduction achieved in patients younger than 18 years old (n=71) at 52 weeks --

-- Regulatory submissions in the U.S. and EU anticipated to be completed in the third quarter of 2025 --

-- Company to host conference call today at 8 a.m. ET --

BOSTON, April 07, 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 positive topline results from the pivotal Phase 3 TRANSCEND trial evaluating setmelanotide, a melanocortin-4 receptor (MC4R) agonist, for the treatment of acquired hypothalamic obesity. The global trial met its primary endpoint with a statistically significant and highly clinically meaningful reduction in body mass index (BMI) with setmelanotide in both adult and pediatric patients versus placebo.

Highlights from the topline data include:

- -19.8% placebo-adjusted difference in 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); and
- 80% of patients on setmelanotide achieved BMI reduction of 5% or greater at 52 weeks.

“Acquired hypothalamic obesity is a serious disease resulting from damage to the hypothalamus, often due to brain tumors or their treatment or certain other injuries resulting in accelerated weight gain, hyperphagia and reduction in energy expenditure. There is an urgent need for effective treatments as current approaches, including lifestyle interventions and pharmacotherapy intended for general obesity, have shown limited effectiveness in achieving long-term, durable weight loss,” said Susan Phillips, MD, pediatric endocrinologist at Rady Children's Hospital-San Diego and professor of pediatrics at UC San Diego School of Medicine. “These data are highly clinically meaningful, offering hope that a new targeted therapy may become available for patients – both adults and children – living with acquired hypothalamic obesity.”

The global Phase 3 TRANSCEND trial is believed to be the largest and longest placebo-controlled trial to evaluate a therapy for patients with acquired hypothalamic obesity. The double-blinded, 52-week trial enrolled 120 patients, randomized 2:1. In addition to the primary endpoint and other data points above, clinically meaningful improvements were observed across key secondary endpoints at week 52, including:

- 83% percent of patients on setmelanotide therapy achieved 5% or greater reduction in BMI (n=33 patients 18 or older) or BMI Z-score reduction of 0.2 or greater points (n=48 patients younger than 18); and
- -1.4 placebo-adjusted mean change in weekly average of the daily maximal hunger score for patients 12 years old or older (n=81) (p=0.003).

No new safety signals with setmelanotide were observed, in line with setmelanotide’s well-established and well-understood safety profile. Consistent with prior clinical experience, setmelanotide was generally well tolerated in the TRANSCEND study. The most common treatment-emergent adverse events (affecting >20% of participants) were nausea, vomiting, diarrhea, injection site reaction, skin hyperpigmentation and headache. No serious adverse events leading to study discontinuation were reported.

“This 12-month placebo-controlled trial required an incredible commitment from patients, their families and clinical staff for which we are extremely grateful. The highly clinically meaningful results from the TRANSCEND study potentially represent a transformational milestone for Rhythm,” said David Meeker, M.D., Chairman, President and Chief Executive Officer of Rhythm. “Given these compelling new efficacy data with setmelanotide in a broader patient population than in our Phase 2 trial, we are

preparing to submit a supplemental New Drug Application to the FDA and a Type II variation request to the European Medicines Agency in the third quarter of 2025. These planned submissions could pave the way for setmelanotide to become the first-ever approved therapy for these patients. In addition, these strong results with an MC4R agonist increase our confidence in the development of our next-generation MC4R agonists, currently in ongoing Phase 1/2 clinical trials in acquired hypothalamic obesity."

Rhythm anticipates presenting full data from the TRANSCEND study at an upcoming medical meeting.

Conference Call Information
Rhythm Pharmaceuticals will host a live conference call and webcast at 8:00 a.m. ET today to discuss these clinical data. Participants may register for the conference call here. 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 at least 30 days following the call.

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 with acquired hypothalamic obesity. A total of 120 patients age 4 years and older were randomized 2:1 to either a daily subcutaneous injection of setmelanotide (80 patients) or placebo (40 patients). The primary endpoint was mean percent change in body mass index (BMI) from baseline after 52 weeks of treatment. Secondary endpoints assess daily hunger, hyperphagia (extreme unsatisfied drive to consume food), weight, quality of life and safety and tolerability. A supplemental cohort of 12 Japanese patients remains ongoing with completion and topline data anticipated in the first quarter of 2026.

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.

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.

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 and 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 anticipated supplemental New Drug Application to the FDA and a Type II variation request to the European Medicines Agency; the estimated market size and addressable population for our drug products, including setmelanotide for the treatment of hypothalamic obesity; the future announcement of data from our other ongoing clinical trials, including the Japanese cohort of our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity; our participation in and presentation of the full data from the TRANSCEND study at an upcoming medical meeting; and the timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may", "will", "aim" 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 ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, positive results from earlier clinical trials of setmelanotide may not be predictive of the results of later clinical trials of setmelanotide, interim, topline and preliminary data that we announced may change as more patient data become available, setmelanotide may cause undesirable side effects that could delay or prevent additional regulatory approvals or limit the commercial profile of approved labeling, Breakthrough Therapy designation by the FDA may not lead to a faster development, regulatory review or approval process, and nor does it increase the likelihood that setmelanotide will receive additional marketing approvals in the United States, failure to identify and develop additional product candidates, 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, the impact of competition, risks related to the commercialization and market acceptance of IMCIVREE for the treatment of hypothalamic obesity in the medical community and with third-party payors, 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, 2024 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 press release or to update them to reflect events or circumstances occurring after the date of this press release, whether as a result of

new information, future developments or otherwise.

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