Rhythm Pharmaceuticals Announces New Data Presentations on Patients with Acquired or Congenital Hypothalamic Obesity (N=35) Treated with Setmelanotide for up to Nine Months in French Early-access Program

May 14, 2025

-- New data showed setmelanotide achieved consistent, meaningful weight reduction --

-- Multiple presentations delivered at the first-ever Joint Congress between the European Society for Paediatric Endocrinology and the European Society of Endocrinology (ESPE-ESE); 32nd annual European Congress on Obesity (ECO); and the 2025 annual meeting of the Pediatric Endocrine Society (PES 2025) --

BOSTON, May 14, 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 the presentation of new, real-world data at two European congresses that show consistent improvements in body mass index (BMI), BMI-z, and hunger scores in a total of 35 patients with acquired or congenital hypothalamic obesity who were treated with setmelanotide for up to nine months.

Physicians from Sorbonne University in Paris delivered two oral presentations with data from patients in the early-access programs in France. At the first-ever Joint Congress between the European Society for Paediatric Endocrinology and the European Society of Endocrinology (ESPE-ESE), the presentation detailed real-world data from 30 patients with acquired hypothalamic obesity on setmelanotide therapy for up to nine months. For the second presentation at the 32nd annual European Congress on Obesity (ECO), they also shared data from five patients with congenital hypothalamic obesity, including four patients who reached six months on setmelanotide therapy.

“These real-world data show that patients with acquired or congenital hypothalamic obesity on setmelanotide treatment achieved clinically meaningful weight reductions and reductions in hunger beginning at three months that were sustained and deepened in those patients who reached six and nine months on therapy,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “There is a significant unmet need for a treatment that can address the weight gain and overwhelming hunger that patients with either acquired or congenital hypothalamic obesity live with, and we believe these data – which are consistent with data from our Phase 2 and 3 clinical trials – are supportive of the potential efficacy MC4R agonists can achieve for these patients.”

Real-world setmelanotide weight outcomes in French patients with acquired or congenital hypothalamic obesity
The presentations delivered at ESPE-ESE and ECO 2025 detailed clinical outcomes from 30 patients (10 patients younger than 18; 20 patients 18 or older) with acquired hypothalamic obesity who received setmelanotide treatment as part of the pre-approval, early-access program at 14 different treatment centers in France. Highlights include:

- Of the 20 adult patients with acquired hypothalamic obesity treated with setmelanotide therapy:
  - Across all patients, there was an overall -11.9% mean change in body mass index (BMI) from baseline at month 3;
  - Ten (n=10) who reached month 6 on therapy achieved -19.2% mean change in BMI; and
  - Eight (n=8) who reached month 9 on therapy achieved -23.0% mean change in BMI; and
  - Adult patients reported meaningful decreases in hunger scores after 3 and 6 months of treatment with setmelanotide.
- For pediatric patients with acquired hypothalamic obesity treated with setmelanotide, BMI z-score (a measure that represents standard deviations of a child’s BMI that corrects for age and sex) decreased from baseline at all timepoints analysed. A clinically meaningful reduction in BMI z-score is defined as a ≥0.2-point reduction. Data from these pediatric patients include:
  - Ten (n=10) pediatric patients who reached month 3 on therapy achieved a mean BMI z-score decrease of 0.3 from baseline;
  - Seven (n=7) pediatric patients who reached month 6 on therapy achieved a mean BMI z-score decrease of 0.4 decrease from baseline; and
  - Two (n=2) pediatric patients who reached month 9 on therapy achieved a mean BMI z-score decrease of 0.4 from baseline.

The presentation at ECO 2025 also featured data from five patients (4 younger than 18; 1 older than 18) with congenital

hypothalamic obesity. Highlights include:

- Four (n=4) pediatric patients who reached month 3 on setmelanotide therapy achieved a mean BMI z-score decrease of -0.2 from baseline; and
- Three (n=3) pediatric patients who reached month 6 on setmelanotide therapy achieved a mean BMI z-score decrease of -0.4 from baseline; and
- One adult patient with congenital hypothalamic obesity achieved a -14.8% BMI reduction baseline at month 6 of setmelanotide therapy.

Setmelanotide was generally well tolerated with the most frequent AEs being injection site reactions and skin hyperpigmentation. No new safety signals related to use of setmelanotide were observed, consistent with setmelanotide's well-established and well-understood safety profile. For further information about setmelanotide's safety profile, please see the information below under "WARNINGS AND PRECAUTIONS".

Additional Congress Presentations
Additional Rhythm presentations were also shared at ECO and ESPE/ESE. Two presentations will also be shared at the Pediatric Endocrinology Society (PES) annual meeting from May 15-18 in National Harbor, Maryland.

ECO 2025
Rhythm and its collaborators also presented one encore oral presentation, three encore poster presentations and hosted one satellite symposium at ECO:

- "DAYBREAK Trial: Setmelanotide vs placebo in patients with Melanocortin-4 Receptor Pathway Variants"
- "Frequency of Bardet-Biedl syndrome variants in a population with early-onset obesity"
- "Weight loss at 18 months of setmelanotide in 2 to <6-year-old patients with rare MC4R pathway diseases"
- "Body composition improvements with 12 months of setmelanotide in acquired hypothalamic obesity"

ESPE-ESE 2025
In addition to sharing the acquired hypothalamic obesity data from the French early-access program, Rhythm and its collaborators also presented two poster presentations and two oral presentations and hosted a satellite symposium at the conference.

- "Setmelanotide treatment in individuals with obesity and PHIP variants: Results from the DAYBREAK trial"
- "Patient and caregiver experiences with setmelanotide treatment in Bardet-Biedl syndrome – real-world evidence and a patient support program"
- "Age of onset of hyperphagia and/or obesity as key predictors of a positive genetic test for POMC, PCSK1 or LEPR deficiency or BBS"
- "Weight loss at 18 months of setmelanotide in 2 to <6-year-old patients with rare MC4R pathway diseases"

PES 2025
Rhythm and its collaborators will present two posters at the 2025 Pediatric Endocrine Society (PES) Annual Meeting held May 15-18, 2025 in National Harbor, Maryland:

- "Impact of setmelanotide on metabolic syndrome risk score in pediatric patients with acquired hypothalamic obesity"
- "Clinical characteristics of 2 to 5-year-old patients with hyperphagia and obesity secondary to melanocortin-4 receptor pathway diseases and 1-year response to setmelanotide"

All of the Rhythm-related presentations from ECO, ESPE-ECE, and PES are available here: https://hcp.rhythmtx.com/publications-presentations/. These presentations are intended for U.S. audiences.

Rhythm previously announced that its pivotal Phase 3 trial evaluating setmelanotide for the treatment of acquired hypothalamic obesity met its primary endpoint with a -19.8% placebo-adjusted BMI reduction in 120 patients. The Company remains on track to submit a supplemental New Drug Application to the FDA and a Type II variation request to the European Medicines Agency for setmelanotide for the treatment of patients with acquired HO in the third quarter of 2025. In addition, Rhythm anticipates it will complete enrollment in the Phase 3 trial substudy investigating the use of setmelanotide in congenital hypothalamic obesity in the second 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) 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 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 the safety, efficacy, potential benefits of, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of 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 planned substudy to evaluate patients with congenital hypothalamic obesity and the timing of enrollment for the substudy to our Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity; 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 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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