Rhythm Pharmaceuticals Announces Five Presentations at ESPE 2024, including New Real-world Data in Pediatric Patients with Acquired or Congenital Hypothalamic Obesity Treated with Setmelanotide

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-- Four Pediatric patients treated in French early-access program achieved meaningful weight reduction at three months on setmelanotide therapy --

-- Rhythm announced plans for a new substudy to evaluate setmelanotide therapy in patients with congenital hypothalamic obesity --

BOSTON, Nov. 18, 2024 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a 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 that showed four pediatric patients with acquired hypothalamic obesity or congenital hypothalamic obesity achieved >5% weight reduction at three months on setmelanotide, a melanocortin-4 receptor (MC4R) agonist. These data were among five Rhythm-related presentations delivered during the 62nd annual meeting of the European Society for Paediatric Endocrinology (EPSE) in Liverpool, England.

“Patients living with hypothalamic obesity – whether acquired or congenital –are mostly refractory to lifestyle programs and anti-obesity medicines that do not address the underlying cause,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “Based on these case reports and insight generated through our pre-approval early-access program for setmelanotide in France, we look forward to exploring the potential efficacy of setmelanotide to offer a new therapy for these patients.”

3-month real-world setmelanotide hunger and weight outcomes in four French pediatric patients with acquired or congenital hypothalamic obesity
The presentation includes results from four case reports of patients <18 years old, two with acquired hypothalamic obesity and two with congenital hypothalamic obesity, at month three on setmelanotide therapy:

- Congenital hypothalamic obesity:
  - Female, age 15, with septo-optic dysplasia as cause of hypothalamic obesity, achieved a body weight decrease of 9.6% from baseline (94 kg) at month 3 and BMI-Z score change from 3.1 at baseline to 2.8;
  - Male, age 9, with pituitary stalk interruption syndrome (PSIS) as cause of hypothalamic obesity, achieved a body weight decrease of 5.2% from baseline (64 kg) at month 3 and BMI-Z score change from 3.7 at baseline to 3.5;
- Acquired hypothalamic obesity:
  - Male, age 13, with acquired hypothalamic obesity related to craniopharyngioma resected at age 9, achieved a body weight decrease of 5.6% from baseline (116 kg) at month 3 and 9.5% weight reduction at month 6, and BMI-Z score change from 3.7 at baseline to 3.4 at month six of setmelanotide therapy; and
  - Male, age 13, with acquired hypothalamic obesity related to radiotherapy for juvenile pilocytic astrocytoma, achieved a body weight decrease of 8.3% from baseline (88.3 kg) at month 3 and BMI-Z score change from 3.1 at baseline to 2.8.

These patients were treated with setmelanotide at four different hospitals in France under a pre-marketing, early-access authorization program. All four patients remain on therapy, as of November 15, 2024, and there were no new safety signals observed.

“These patients present with differences and complexities associated with hypothalamic obesity, but these conditions share the same disrupted MC4R pathway signaling,” said Dr. Ahlam Azar-Kolakez, MD, Endocrinology-Diabetology Department, Reference Center for Endocrine Growth and Developmental Diseases, Robert Debré Hospital, Assistance Publique-Hôpitaux de Paris, France. “These real-world results are the first reported evidence of setmelanotide treatment for patients with congenital hypothalamic obesity demonstrating that it may be an effective, targeted therapy for both acquired and congenital hypothalamic obesity despite differences in etiology.”

Also today, Rhythm announced plans for a new, 34-week substudy designed to evaluate setmelanotide in 39 patients with congenital hypothalamic obesity aged 4 years and older. Rhythm is seeking approval from the U.S. Food and Drug Administration (FDA) for the independent substudy for congenital hypothalamic obesity as a protocol amendment to the Company’s ongoing Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity. Rhythm anticipates enrolling the first

patients with congenital hypothalamic obesity in the first quarter of 2025.

The substudy in congenital hypothalamic obesity is independent from Rhythm's pivotal Phase 3 trial in acquired hypothalamic obesity. The Company remains on track to disclose topline data from that pivotal trial in the first half of 2025.

About Congenital Hypothalamic Obesity
Congenital hypothalamic obesity is a rare disease caused by certain inborn brain abnormalities that may impair the function of the MC4R pathway, which regulates satiety or food intake and energy expenditure. The hallmark features of this disease include hyperphagia and early-onset, refractory obesity that is often linked to an impairment in the MC4R pathway associated with several pituitary deficiencies. Rare diseases that may cause congenital hypothalamic obesity include septo-optic displasia (or de Morsier syndrome), optic nerve hypoplasia, multiple pituitary hormone deficiency (also known as combined pituitary hormone deficiency) and pituitary stalk interruption syndrome. Each of these diseases is considered rare, and between 12% and 40% of patients with these diseases may have congenital hypothalamic obesity. Rhythm's preliminary estimate of the prevalence of congenital hypothalamic obesity is in excess of 1,000 patients in the United States with a similar prevalence in Europe.

Additional Presentations at ESPE 2024
In a poster entitled, "Evaluating Setmelanotide Treatment for 12 Months in Pediatric Age Groups With Rare Melanocortin-4 Receptor Pathway–Related Obesity: Efficacy in Weight Reduction and Safety Outcomes," presenters highlighted the importance of early intervention in young patients with rare MC4R pathway diseases. A cross-sectional analysis of 50 patients aged 2 to 17 years with rare MC4R pathway diseases who participated in one of five different clinical trials of setmelanotide was presented showing that patients regardless of age achieved clinically meaningful weight reductions, and that children between 2 and 5 years old achieved a greater absolute BMI Z reduction.

Additionally, the Company delivered three oral presentations based on analyses of more than 5,000 sequencing samples from the Company's European genetic testing program for individuals with suspected rare MC4R pathway diseases, Rare Obesity Advanced Diagnosis or ROAD®. Genetic testing of individuals with early-onset obesity can help improve disease etiology understanding and identify patients who may benefit from specialized care.

Highlights from these three presentations included:

- 1.74% of individuals tested carried a biallelic variant in one of 22 tested genes related to Bardet-Biedl syndrome (BBS), and the frequency in Turkey was 5.82%, potentially due to consanguinity rates;
- 22.5% of tested individuals with early-onset obesity carried a variant classified as pathogenic, likely pathogenic or of unknown significance (VUS) of one or more genes closely associated with MC4R pathway function: *SIM1, SEMA3* family, *PLXNA* family, *POMC, PCSK1, LEPR, SH2B1* and *NCOA1*; and
- 4.9% of tested individuals carried a biallelic or heterozygous pathogenic, likely pathogenic or VUS variant in one or more of these genes: *ALMS1*, *BBS*, *MAGEL2*, *PHIP*, or *TBX3* genes. These genes are associated with certain debilitating syndromes.

All of the Rhythm-related presentations from ESPE 2024 are 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) 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. The EC has also authorized setmelanotide for control of hunger and treatment of obesity in children as young as 2 years old, living with BBS or POMC, PCSK1, or LEPR deficiency. 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 2 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 U.S. Prescribing Information and EU Summary of Product Characteristics 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, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of setmelanotide and other product candidates; the timing of results from our global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity; the planned new substudy to the ongoing Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity that would add and evaluate patients with congenital hypothalamic obesity and the timing of enrollment for the substudy; 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, POMC, PCSK1, or LEPR variants or genetically confirmed Bardet-Biedl syndrome (BBS); expectations surrounding potential clinical trial results, regulatory submissions and approvals; our participation in upcoming events and presentations, the 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 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, 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 Rhythm’s Quarterly Report on Form 10-Q for the three months ended September 30, 2024 and 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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