Rhythm Pharmaceuticals Presents Data Demonstrating BMI Reduction in Patients with Hypothalamic Obesity Treated with Setmelanotide over Six Months at ENDO 2023

June 17, 2023

-- Mean BMI reduction of 21.0% from baseline observed in 13 patients at six months, showing progression from 16.8% mean BMI reduction at 16 weeks --

-- Phase 3 trial evaluating setmelanotide in acquired hypothalamic obesity ongoing; completion of enrollment expected 1Q 2024 --

BOSTON, June 17, 2023 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases, today announced data that showed meaningful weight loss was sustained and progressed in patients with hypothalamic obesity treated with setmelanotide for six months as part of the long-term extension of its Phase 2 trial.

“Hypothalamic obesity is a challenging disease to manage with patients generally refractory to standard treatments for obesity. The setmelanotide results to date have been remarkable with setmelanotide demonstrating sustained and deepening reductions in multiple body mass index (BMI) measures at six months of treatment, showing progressive and consistent improvement over previously reported 16-week BMI reduction data,” said Christian Roth, M.D., Seattle Children’s Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington, who presented these data during The Endocrine Society Annual Meeting & Expo (ENDO 2023) being held June 15-18 in Chicago. “This impressive response adds to the evidence suggesting setmelanotide may provide a meaningful clinical benefit for patients with this disease who currently have no approved therapeutic options.”

Rhythm enrolled 18 patients in its open-label, 16-week Phase 2 trial designed to evaluate setmelanotide in patients with acquired hypothalamic obesity. Thirteen of those patients[1] who enrolled in the long-term extension trial reached a total of six months or more on setmelanotide therapy, as of the data cutoff date of Nov. 30, 2022. Highlights from the data presented show:

- 21.0 mean percent reduction in BMI at month 6 from baseline, which progressed from 16.8 mean percent reduction in BMI at week 16 across these 13 patients;
- 10 of 13 (76.9%) patients achieved 10% BMI reduction or greater at month 6 and all 13 patients achieved 5% BMI reduction or greater;
- 9.2 kg (23.9%) and 3.0 kg (6.3%) mean decreases observed in fat mass and lean muscle mass, respectively, at week 16 in pediatric patients (n=11); and
- 1.7 point mean decrease from baseline in BMI-Z score from baseline in patients younger than 18 (n=11).

In addition, Rhythm presented data demonstrating that all patients achieved improvement in severity of their obesity, and 10 of 13 patients achieved an improvement in weight classification by one or more class, as defined by the U.S. National Institutes of Health and the World Health Organization, which characterize obesity classes based on BMI[2]. Among pediatric patients, there was a 34.3 percentage point decrease in the 95th percentile at month 6, which corresponds to an average move from morbid obesity to mild obesity.

Consistent with prior clinical experience in other rare MC4R pathway diseases, setmelanotide was observed to be generally well tolerated and no new safety concerns were observed in the long-term extension trial, as of the cutoff date Nov. 30, 2022.

Additional presentations
Rhythm and its collaborators presented three additional posters at ENDO 2023:

As presented in a poster titled, “Treatment History and Comorbidities Reported by Patients with Hypothalamic Obesity Treated with Setmelanotide in a Phase 2 Trial,” 78% of patients with hypothalamic obesity who had participated in that trial had attempted and failed lifestyle modifications, such as diet modification and calorie restriction, before enrolling in this trial. A total of nine patients had used and failed to achieve weight loss with pharmacotherapies, including seven who tried using multiple anti-obesity medications.

Data presented on a poster entitled, “Effect of Setmelanotide on Metabolic Parameters and Vital Signs in a Phase 2 Trial of Patients with Hypothalamic Obesity,” showed that most patients experienced reduction in waist circumference with favorable changes in body composition and no adverse changes in metabolic, glycemic, or vital sign parameters.

Also presented was, “Trial Design of a Double-blind, Randomized, Placebo-Controlled, Phase 3 Study of Setmelanotide in Patients with Hypothalamic Obesity.” This ongoing pivotal trial is designed to enroll 120 patients 4 years old or older randomized 2:1 to setmelanotide therapy or placebo for a total of 60 weeks, including up to eight weeks for dose titration. The primary endpoint is the percent change in BMI after approximately 52 weeks on a therapeutic regimen of setmelanotide versus placebo. Rhythm expects to complete patient enrollment in the first quarter of 2024.

All Rhythm’s presentations from ENDO will be available on the Publications and Presentations section of its website: https://www.rhythmtx.com/publications/.

About Hypothalamic Obesity
Hypothalamic obesity is a rare, acquired form of extreme obesity that occurs following damage to the hypothalamic region of the brain, which includes the 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 in the first six to 12 months following tumor resection, and ultimately develop severe obesity. In addition, people living with hypothalamic obesity may also experience delayed puberty and infertility, decreased physical activity, excessive daytime sleepiness, attention hyperactivity disorder, seizures and psychiatric conditions. Based on an analysis of incidence rates and prevalence reports of certain brain tumor types, as well as survival and obesity rates tied to these brain tumor types, Rhythm estimates there are approximately 5,000-10,000 patients living with hypothalamic obesity in the U.S. with approximately 500 new cases each year. There are no FDA approved therapies for hypothalamic obesity.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) diseases. Rhythm's lead asset, IMCIVREE ® (setmelanotide) is approved by the U.S. Food and Drug Administration (FDA) and authorized by the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) for use in accordance with product labeling. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare MC4R pathway diseases, as well as a preclinical suite of investigational candidates 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 Bardet-Biedl syndrome (BBS) or genetically confirmed loss-of-function biallelic proopiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

In Canada, setmelanotide is indicated for the treatment of obesity due to Bardet-Biedl syndrome (BBS) or genetically-confirmed biallelic pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency due to variants interpreted as pathogenic, likely pathogenic, or of uncertain significance in adults and children 6 years of age and above.

Limitations of Use
In the United States and Europe, Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

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.

WARNINGS AND PRECAUTIONS

Skin Monitoring: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing naevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and during treatment with setmelanotide.

Heart rate and blood pressure monitoring: 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.

Prolonged penile erection: Spontaneous penile erections have been reported in clinical trials with setmelanotide. Patients who have a penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment of priapism.

Depression: In clinical trials, depression has been reported in patients treated with setmelanotide. Patients with depression should be monitored at each medical visit during treatment with setmelanotide. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.

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. The prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Excipients: This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Patients who are pregnant or breastfeeding should be advised of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. This medicinal product should be used with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free."

ADVERSE REACTIONS
The most frequent adverse reactions are hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache (26%).

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no data from the use of setmelanotide in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-fetal effects. As a precautionary measure, setmelanotide should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in fetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide treatment as there was no proof of teratogenicity in the nonclinical data. If a patient who is taking setmelanotide and still losing weight gets pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring for the recommended weight gain during pregnancy. The treating physician should carefully monitor weight during pregnancy in a patient taking setmelanotide.

Breast-feeding
It is unknown whether setmelanotide is excreted in human milk. A nonclinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from setmelanotide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility
No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337. See Summary of Product Characteristics' APPENDIX V for a list of European national reporting systems to communicate adverse reactions.

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 U.S. 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 of setmelanotide, including with respect to the Phase 2 clinical trial evaluating setmelanotide in hypothalamic obesity, the long term extension trial, and the anticipated timing of a Phase 3 trial, the potential benefits of setmelanotide for patients, including those with hypothalamic obesity, and our expectations surrounding potential regulatory submissions, approvals and timing thereof, our business strategy and plans, including regarding commercialization of setmelanotide, and our participation in upcoming events and presentations. 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, 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 liquidity and expenses, the impact of the COVID-19 pandemic and general economic conditions on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the three months ended March 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.

Corporate Contact:
David Connolly
Head of Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

Investor Contact:
Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannah.deresiewicz@sternir.com

Media Contact:
Adam Daley
Berry & Company Public Relations
212-253-8881
adaley@berrypr.com

[1] Six-month data is not available for a 14th patient who transitioned from the Phase 2 trial and enrolled in the open-label, long-term extension trial was lost to follow up. This patient has reentered the long-term extension trial and was undergoing dose escalation as of Nov. 30, 2022.

[2] Class III – BMI ≥ 40 kg/m^2 (also referred to as severe, extreme, or massive obesity); Class II – BMI 35 to 39.9 (severe obesity); Class I – BMI 30 to 34.9 (mild obesity); In pediatric patients, all three obesity classes are ≥95th percentile. (https://www.nhlbi.nih.gov/health/overweight-and-obesity/symptoms)

Source: Rhythm Pharmaceuticals, Inc.