Rhythm Pharmaceuticals Presents Data from Phase 2 and Long-term Extension Trials Evaluating Setmelanotide for the Treatment of Hypothalamic Obesity at ObesityWeek® and Plans to Initiate Phase 3 Trial in Early 2023

November 2, 2022

-- Phase 3 clinical trial design reflects feedback obtained during recent discussions with FDA --

*-- 89 percent (16 of 18) patients achieved primary endpoint with a BMI decrease greater than 5 percent at 16 weeks on setmelanotide therapy (*P<0.0001) –

-- Long-term data show sustained and increasing weight loss out to 41 weeks --

-- Management to host conference call at 8:30 a.m. ET today --

BOSTON, Nov. 02, 2022 (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 positive Phase 2 results and long-term extension trial data in hypothalamic obesity that are being presented today as a late-breaking poster at The Obesity Society's ObesityWeek ® 2022 conference in San Diego.

In addition, Rhythm today announced the design of its Phase 3 clinical trial in acquired hypothalamic obesity, which is anticipated to initiate in early 2023, following recent discussions with the U.S. Food & Drug Administration (FDA). As announced this week, the FDA granted Breakthrough Therapy designation to setmelanotide for the treatment of hypothalamic obesity.

"Hypothalamic injury can result from surgery or radiation for a benign tumor and often leads to sudden weight gain, a loss of energy and appetite changes, all of which are unresponsive to existing therapies," said Christian Roth, M.D., Seattle Children's Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington. "These Phase 2 data and long-term extension trial data show that setmelanotide can achieve a rapid and sustained reduction in body weight, potentially representing a major advancement in the development of a much-needed therapy for patients with hypothalamic obesity."

The Phase 2 study enrolled 18 patients with hypothalamic obesity caused by structural hypothalamic damage secondary to craniopharyngioma or other benign brain tumor types, surgical resection, and/or chemotherapy. Patients were between 6 and 40 years old with a body mass index (BMI) ≥95th percentile (children 6 to <18 years) or ≥35 kg/m^2 (adults ≥18 years). The primary endpoint was the proportion of patients who achieved a 5 percent or greater reduction in BMI after 16 weeks of treatment. Hunger was also assessed daily, as self-reported by individual patients. Highlights from the data include:

- 89 percent (16 of 18) patients evaluable for assessment had ≥5% reduction in BMI (P<0.0001; confidence interval, 69%-98%);
- 78 percent (14 of 18) patients had a 10% or greater reduction in BMI at 16 weeks;
- 14.5 mean percent reduction in BMI (N=18) at Week 16 from baseline;
- 12.6 mean percent reduction body weight (N=18) at Week 16 from baseline;
- Mean (standard deviation [SD]) BMI Z score at Week 16 was 2.7 (1.3) (n=13 pediatric patients), a reduction of 1.3 (1.0) points from baseline; and
- Mean (SD) most hunger score at baseline was 6.6 (1.6), compared with 3.7 (2.5) at Week 16, for a reduction of –2.9 (2.3) points or 45% for patients ≥12 years of age (n=11).

Consistent with prior clinical experience in other rare MC4R pathway diseases, setmelanotide was observed to be generally well tolerated. The most common adverse events (AEs) included nausea (61.1%), vomiting (33.3%), skin hyperpigmentation (33.3%), diarrhea (22.2%), and COVID-19 (22.2%). Two patients discontinued due to AEs and a third patient was non-compliant.

Long-term Extension Data

The ObesityWeek® poster also included data on patients who continued on setmelanotide therapy in Rhythm's open-label, long-term extension trial after completing 16 weeks on setmelanotide therapy in the Phase 2 trial. A total of 14 patients continued on therapy in this long-term extension trial. As of a cut-off date of September 23, 2022, of these patients:

- 13 patients who reached a total of 29 weeks on setmelanotide therapy achieved a mean BMI reduction of 21.1% (SD, 11.2%); and
- Five (5) patients who reached a total of 41 weeks on setmelanotide therapy achieved a mean BMI reduction of 26.7% (SD, 12.4%).

Phase 3 Trial to Initiate in Early 2023

Rhythm's Phase 3 clinical trial in acquired hypothalamic obesity will enroll 120 patients aged 4 years 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 will be the percent change in BMI after approximately 52 weeks on a therapeutic regimen of setmelanotide versus placebo. Key secondary endpoints will include the proportion of patients who achieve ≥5% reduction in BMI from baseline in adults (≥18) or BMI Z-score reduction of ≥0.2 from baseline in pediatrics after approximately 52 weeks on a therapeutic regimen of compared with placebo; and mean change in the weekly average of the daily most hunger score in patients ≥12 years from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide versus placebo.

"Setmelanotide has shown significant potential to transform the care of individuals living with the onset of extreme weight gain from hypothalamic obesity. This serious condition affects approximately 5,000 to 10,000 individuals in the United States alone and we believe that setmelanotide could represent an opportunity to substantially improve medical outcomes for this group," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "These latest exciting results, which suggest that setmelanotide results in significant, durable weight loss, coupled with the Breakthrough Therapy Designation from the FDA, fuel our urgency to continue executing on our development strategy for hypothalamic obesity and additional MC4R pathway diseases."

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.

Conference Call Information

Rhythm will host a live conference call and webcast at 8:30 a.m. ET today to discuss these data. Participants may register for the conference call here. While not required, it is recommended that participants join the call ten minutes prior to the scheduled start.

A live webcast of the call will also be available under "Events and Presentations" in the Investor Relations section of the Company's website at http://ir.rhythmtx.com/. The archived webcast will be available on Rhythm's website approximately two hours after the conference call and will be available for 30 days following the call.

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) pathway diseases. Rhythm's precision medicine, setmelanotide, 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). The European Commission (EC) has 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 UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity and is leveraging the Rhythm Engine and the largest known obesity DNA database -- now with approximately 45,000 sequencing samples -- to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. 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 pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency 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-foetal 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, and our business strategy and plans, including regarding commercialization of setmelanotide. 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 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 quarter ended June 30, 2022 and our other filings with the U.S. 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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