Rhythm Pharmaceuticals Announces First Patients Dosed in DAYBREAK and Weekly Trials Evaluating Setmelanotide for Rare Genetic Diseases of Obesity

January 13, 2022

-- DAYBREAK is the most comprehensive Phase 2 trial ever initiated in rare genetic diseases of obesity --
-- DAYBREAK is evaluating setmelanotide in patients with severe obesity and hyperphagia caused by variants in one of 31 pre-identified genes --
-- First patient also dosed in Phase 3 switch trial evaluating a weekly formulation of setmelanotide --

BOSTON, Jan. 13, 2022 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company committed to transforming the care of people living with rare genetic diseases of obesity, today announced the first patient has been dosed with setmelanotide, the company's melanocortin-4 receptor (MC4R) agonist, in the Phase 2 DAYBREAK clinical trial to treat the severe obesity and hyperphagia potentially caused by a genetic variant that impairs function of the MC4R pathway. The company also announced the dosing of the first patient in the Phase 3 trial evaluating a switch from the daily to a novel weekly formulation of setmelanotide.

The DAYBREAK trial [NCT04963231] is designed to evaluate setmelanotide in patients who carry a confirmed variant in one or more of 31 genes with strong or very strong relevance to the MC4R pathway, which regulates the body's energy balance, including appetite, energy expenditure and body weight. Results from the DAYBREAK clinical trial have the potential to identify future patient populations and to inform the design of future registrational studies to support setmelanotide label expansion.

"With significant advances in gene sequencing and analysis, we have deepened our understanding of the relationship between genetics and severe obesity. However, there remains a significant unmet need with no effective therapeutic options for most patients with rare genetic diseases of obesity," said Sadaf Farooqi, M.D., Ph.D., of the Wellcome-MRC Institute of Metabolic Science at the University of Cambridge, a principal investigator for the DAYBREAK trial and world-renowned expert on genetic obesity. "The DAYBREAK trial is a comprehensive and robust trial designed to evaluate setmelanotide in patients with early-onset, severe obesity and hyperphagia, which may be caused by a genetic impairment of the MC4R pathway."

DAYBREAK is a two-stage, double-blind, placebo-controlled trial that will be conducted at more than 75 trial sites across 12 countries. Rhythm plans to enroll approximately 500 patients (6 to 65 years old) with severe obesity and a variant in one of 31 genes relevant to the MC4R pathway. Any patients who demonstrate a clinically meaningful response to setmelanotide at the end of a 16-week, open-label run-in period will be eligible to enter the second stage of the study. Stage 2 will be a 24-week, double-blind, placebo-controlled withdrawal study, in which patients will be stratified into genetically defined cohorts and randomized 2:1 to receive setmelanotide or placebo.

The primary efficacy endpoint is a responder analysis based on the proportion of patients treated with setmelanotide who achieve a clinically meaningful weight reduction threshold at the end of treatment compared to patients treated with placebo. Each genetically defined cohort can read out results independently.

"DAYBREAK is designed to enable rapid and robust proof-of-concept in multiple genetic cohorts, potentially demonstrating setmelanotide treatment effects on obesity and hunger," said Linda Shapiro, M.D., Ph.D., Chief Medical Officer of Rhythm. "The initiation of DAYBREAK is an exciting milestone in our journey to transform the care and lives of many more people living with rare genetic disorders of obesity."

Rhythm estimates that approximately 35 percent of people living with early-onset, severe obesity may test positive for a genetic variant that would make them eligible to enroll in DAYBREAK. The Company offers Uncovering Rare Obesity® a no-charge, comprehensive genetic testing program for rare genetic diseases of obesity, which can be ordered by physicians in the United States. Rhythm's European program, which is designed to complement existing genetic testing programs, is expected to be available in the first half of 2022.

Phase 3 Weekly Switch Trial Underway

Rhythm also announced today that it has dosed the first patients in the Phase 3 switch trial evaluating a weekly formulation of setmelanotide in patients 6 years of age and older with a rare genetic disease of obesity who are currently taking the daily formulation of setmelanotide.

Rhythm's weekly formulation of setmelanotide is designed to offer patients a more convenient dosing regimen. It is being evaluated in a Phase 3 randomized, double-blind switch trial in patients with obesity due to biallelic or heterozygous POMC, PCSK1 or LEPR genetic variants or a clinical diagnosis of BBS with genetic confirmation, who were previously enrolled in Rhythm's long-term, open-label daily setmelanotide extension trial. Rhythm expects to enroll 30 patients, randomized 1:1 to receive once-weekly setmelanotide and once-daily placebo, or once daily setmelanotide and once weekly placebo for 13 weeks. Following the 13-week randomized treatment period, patients will crossover to an open-label, 13-week study in which all patients will receive once-weekly setmelanotide. The primary efficacy endpoint is a responder analysis, based on the proportion of patients with no weight gain defined as a change of 5 percent or less from baseline to week 13.

Additional Phase 3 Clinical Trials on Track to Initiate in 2022

Rhythm expects to initiate three additional Phase 3 trials of setmelanotide in 2022, including:

- The pivotal Phase 3 EMANATE clinical trial, which is expected to initiate in the first quarter of 2022. EMANATE, a randomized, double-blind, placebo-controlled trial, will evaluate setmelanotide in five independent sub-studies in patients

with obesity due to: a heterozygous variant of the POMC/PCSK1 genes or LEPR gene, certain variants of the SRC1 gene or the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway. The company estimates these populations represent approximately 100,000-200,000 people in the United States.

- The Phase 3 pediatric trial evaluating daily setmelanotide in patients between the ages of 2 and less than 6 years of age with rare genetic diseases of obesity, which is expected to initiate in the first quarter of 2022. Rare genetic diseases of obesity often present early in life, and Rhythm's genetic testing programs have identified many patients with these diseases who are younger than 6 years old. If successful, VENTURE could enable earlier therapeutic intervention, with the potential to change the overall trajectory of disease and transform the lives of these patients and their families. This trial [NCT04966741] is a multi-center, one-year, open-label trial in pediatric patients with obesity due to biallelic POMC, PCSK1 or LEPR deficiency or a clinical diagnosis of BBS with genetic confirmation. The primary efficacy endpoint is a responder analysis, based on the proportion of patients who experience a decrease from baseline in BMI Z of ≥0.2.
- A second Phase 3 trial to evaluate the weekly formulation of setmelanotide, which is expected to initiate in the second half of 2022. This de novo trial will be a randomized, double-blind clinical trial in patients with BBS who live outside the United States. The company expects to enroll 40 patients, randomized 1:1 to receive 30 mg of setmelanotide or placebo once weekly for 18 weeks. Following the 18-week treatment period, patients will continue on treatment, or crossover from placebo to active therapy, for an additional 14 weeks. The primary efficacy endpoint is the mean change from baseline in body weight after approximately 18 weeks of once weekly dosing.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. Rhythm's precision medicine, IMCIVREE (setmelanotide), was approved in November 2020 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 obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing and in July and September 2021, respectively, by the European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) 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. IMCIVREE is the first-ever FDA-approved and EC- and MHRA-authorized therapy for patients with these rare genetic diseases of obesity. The Company submitted a supplemental New Drug Application (sNDA) to the FDA, which was accepted for filing in September November 2021 and assigned a Prescription Drug User Fee Act (PDUFA) goal date of March 16, 2022, and submitted a Type II variation application to the European Medicines Agency in October 2021 seeking regulatory approval and authorization for setmelanotide to treat obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome in both the United States and European Union. 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.

IMCIVREE® (setmelanotide) Indication
In the United States, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency, confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the EU and Great Britain, IMCIVREE is indicated 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. IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Important Safety Information

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with IMCIVREE. Instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Monitor patients for new onset or worsening of depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

Skin Pigmentation and Darkening of Pre-Existing Nevi: IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect. This effect is reversible upon discontinuation of the drug. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary 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.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS
Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Treatment with IMCIVREE is not recommended for use while 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 Full Prescribing Information, EU SmPC and MHRA SmPC for IMCIVREE.

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 of setmelanotide, including with respect to our ongoing DAYBREAK and Phase 3 weekly switch trials and planned EMANATE, VENTURE and Phase 3 *de novo* trials, 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 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 quarterly period ended September 30, 2021 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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Source: Rhythm Pharmaceuticals, Inc.