Rhythm Pharmaceuticals Announces Comprehensive Expansion of Clinical Development Program with Five New Phase 2 and 3 Trials Planned to Evaluate Setmelanotide in Rare Genetic Diseases of Obesity

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-- Pivotal Phase 3 EMANATE trial planned in patients with heterozygous POMC, PCSK1 or LEPR, and SRC1 or SH2B1 deficiency obesities --
-- EMANATE, as well as Phase 2 DAYBREAK trial evaluating setmelanotide in 31 new genes, Phase 3 pediatrics trial and Phase 3 trials of weekly setmelanotide formulation all expected to initiate in 2H 2021 --
-- Updated Uncovering Rare Obesity genetic test with expanded gene panel launched in July --
-- Company to host conference call at 8 a.m. ET today --

CAMBRIDGE, Mass., Aug. 03, 2021 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic diseases of obesity, today announced a significant expansion of its clinical development program for setmelanotide with five new planned Phase 2 and 3 clinical trials. Rhythm will review these updates on its second quarter 2021 financial results and business update conference call today at 8 a.m. ET.

New trials include the pivotal EMANATE Phase 3 trial and the DAYBREAK Phase 2 trial, which together will evaluate setmelanotide in people with variants in one of 36 genes in the melanocortin-4 receptor (MC4R) pathway. Based on genetic sequencing data and setmelanotide response rates achieved in a phase 2 trial, Rhythm estimates that the five genetic indications being studied in the EMANATE trial represent a potential addressable patient population of approximately 100,000-200,000 people in the United States.

In addition, Rhythm plans to initiate a Phase 3 trial in pediatric patients ages 2 to 6 years old, as these genetic diseases often present with severe obesity very early in life. The weekly formulation of setmelanotide, which is designed to improve compliance and adherence, will be studied in two phase 3 trials, including a switch study of patients currently on setmelanotide therapy and a de novo trial in patients with BBS.

The company expects to initiate all five studies in the second half of 2021.

"We are excited to announce the significant expansion of our development program for setmelanotide. With these five clinical trials, we will explore opportunities to extend the reach of our precision medicine to address the needs of many more patients suffering from a rare genetic disease of obesity, as well as the potential to improve convenience for patients and caregivers with a weekly formulation," said Murray Stewart, M.D., Chief Medical Officer of Rhythm Pharmaceuticals. "We are grateful to the FDA and EMA for their responsiveness throughout this process. These rare genetic diseases of obesity are serious, life-threatening diseases that affect children with early-onset, severe obesity. This expansion of our development programs reflects our goal to deliver new options to these patients who otherwise have no approved therapies that specifically address the underlying cause of their obesities. We look forward to continuing this productive dialogue as we initiate these studies and, ultimately, seek to advance setmelanotide toward potential additional registrations."

Pivotal EMANATE Phase 3 Trial and DAYBREAK Phase 2 Trial

Rhythm has reached agreement with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) on the clinical design and primary endpoint of its pivotal Phase 3 EMANATE trial of setmelanotide. The trial will be a randomized, double-blind, placebo-controlled study with five independent sub-studies evaluating setmelanotide in patients with: a variant in one of two alleles in the proopiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1) genes; leptin receptor (LEPR) genes (or heterozygous POMC/PCSK1 or LEPR obesity); certain variants of the SRC1; certain variants of SH2B1 genes; or PCSK1 N221D deletions within the MC4R pathway. Each sub-study will be entirely independent of the others and, if successful, is designed to allow Rhythm to submit separate regulatory submissions to the FDA and EMA.

The company plans to enroll 110 patients in each sub-study, randomized one to one to daily setmelanotide or placebo. The trial will enroll patients from six to 65 years old with a body mass index (BMI) of greater than 30 or above the 95th percentile. The primary efficacy endpoint in each sub-study will be the mean percent change in BMI in response to setmelanotide at 52 weeks as compared to placebo. Secondary endpoints will include responder analyses, assessment of the change in hunger scores, and changes in quality-of-life measures.

Rhythm also announced the final design of its Phase 2 DAYBREAK trial of setmelanotide. The trial will be a two-stage, placebo-controlled study in patients with specific variants within one of 31 genes which the Company believes have “strong” or “very strong” relevance to the MC4R pathway.

The company plans to enroll 500 patients in the first stage of the study and to advance approximately 130 patients into the second stage of the study. The first stage of the study will consist of a 16-week open-label run-in; patients 18 years or older who achieve 5 percent weight loss from baseline, or patients under 18 years who achieve a BMI-Z score decrease of at least 0.1 from baseline during this period will be eligible for enrollment in the second stage of the study. Stage 2 will be a 24-week, double-blind, placebo-controlled, randomized, withdrawal study, in which patients will be randomized 2:1 to receive setmelanotide or placebo. For the more prevalent genes, patients will be stratified by variant classification. The primary efficacy endpoint is a responder analysis by gene, based on the proportion of patients who enter Stage 2 who are responders compared to placebo.

Rhythm expects to conduct EMANATE and DAYBREAK at approximately 75 sites across North America, Europe and the Middle East.

Updated Uncovering Rare Obesity Genetic Test Launched

In order to facilitate patient enrollment, Rhythm launched in July 2021 an improved Uncovering Rare Obesity® (URO) genetic test with an expanded panel. This no-charge genetic testing program now includes 80 genes with ties to obesity, including the 36 genes with documented ties to the MC4R pathway that are being evaluated in EMANATE and DAYBREAK. To date, URO has processed approximately 10,000 patient samples and the yield has been consistent with prior reports. As of August 2021 and since URO was first launched, Rhythm has identified approximately 650 patients who would be eligible for EMANATE or DAYBREAK and who live within a reasonable distance of a target trial site. In addition to an expanded gene panel, Rhythm recently enhanced the program to facilitate test ordering and results reporting, with support for interpretation of results.

Phase 3 Pediatric Trial

Rhythm’s Phase 3 trial in pediatric patients ages 2 to 6 years old will be a multi-center, one-year, open-label trial. The company plans to enroll 10 patients, including five with obesity due to biallelic POMC, PCSK1 or LEPR deficiency and five patients with the clinical diagnosis of Bardet-Biedl syndrome (BBS) and genetic confirmation. All patients enrolled in the trial will have a BMI greater than the 97th percentile and will weigh more than 20 kg at baseline. The primary efficacy endpoint will be a responder analysis, based on the proportion of patients who experience a decrease from baseline in BMI-Z of ≥0.2.

Phase 3 Switch and Phase 3 *De Novo* Trials of Weekly Formulation

Rhythm will evaluate its weekly formulation of setmelanotide in two simultaneous Phase 3 trials, including a switch study and a *de novo* trial.

The switch study will be a randomized, double-blind clinical trial in patients with BBS, biallelic or heterozygous POMC, PCSK1 or LEPR deficiency. 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, the trial will crossover to an open-label, 13-week study in which all patients will receive once-weekly setmelanotide. The primary efficacy endpoint will be 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.

The *de novo* trial will be a randomized, double-blind clinical trial in patients with BBS. The company expects to enroll 20 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 will be the mean change from baseline in body weight after approximately 18 weeks of once weekly dosing.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8:00 a.m. ET today to discuss this update, as well as review its second quarter 2021 financial results and recent business activities. The conference call may be accessed by dialing (844) 498-0570 (domestic) or (409) 983-9726 (international), and referring to conference ID 6776764. A webcast of the call will be available under "Events and Presentations" in the Investor Relations section of the Rhythm Pharmaceuticals website at http://ir.rhythmtx.com/. The archived webcast will be available on Rhythm Pharmaceuticals’ 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 treatment paradigm for people living with rare genetic diseases of obesity. The Company’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 by the European Commission (EC) in July 2021 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-authorized therapy for patients with these rare genetic diseases of obesity. Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity. The

Company is leveraging the Rhythm Engine and the largest known obesity DNA database - now with approximately 37,500 sequencing samples - to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. The company is based 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. The condition must be 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, IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with 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
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 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 the anticipated timing for initiation of clinical trials and release of clinical trial data 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, the impact of our management transition, 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 June 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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