Rhythm Pharmaceuticals Optimizes Design of EMANATE and DAYBREAK Clinical Trials to Advance Setmelanotide for Rare Genetic Diseases of Obesity

April 6, 2022

– Phase 3 EMANATE trial to focus on rare patient populations with highest likelihood for success –

– First patient enrolled in EMANATE –

– Ongoing Phase 2 DAYBREAK trial to focus initially on 10 genes with strongest relevance to the MC4R pathway –

– Trial and other program changes extend cash runway into 4Q2023 –

BOSTON, April 06, 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 modifications intended to optimize its Phase 3 EMANATE and ongoing Phase 2 DAYBREAK trials to focus on rare patient populations, which the Company believes have the highest likelihood of success. These changes are intended to optimize the design of each clinical trial, with the goal of most efficiently advancing setmelanotide as a precision medicine for patients with rare genetic diseases of obesity.

The EMANATE trial now includes four independent sub-studies evaluating setmelanotide, the Company's melanocortin-4 receptor (MC4R) agonist, in patients with obesity due to a heterozygous variant of the *POMC/PCSK1* genes, the *LEPR* gene, the *SRC1* gene and the *SH2B1* gene. Rhythm estimates that patients with rare variants in these genes represent a potential addressable U.S. population of approximately 53,000, based on internal genetic sequencing data. The Company also announced today that the first patient has been enrolled in the EMANATE trial.

Recent feedback from the U.S. Food and Drug Administration (FDA) indicated that additional clinical trials to support potential registration for non-rare patient populations would likely be required. As a result, Rhythm eliminated a fifth sub-study, intended to evaluate setmelanotide in patients with a PCSK1 N221D variant. In the POMC/PCSK1 and LEPR sub-studies, the Company will focus enrollment on heterozygous variants classified as pathogenic and likely pathogenic, as initially planned. In addition, instead of enrolling across the entire spectrum of variants of uncertain significance (VUS), Rhythm will focus on patients with suspected pathogenic variants, or a subset of VUS, which are most likely to impair MC4R pathway function.

"We believe these modifications improve the likelihood of success for EMANATE's independent sub-studies by focusing exclusively on rare patient populations with an efficient path to potential registration," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "With FDA feedback, we made a strategic decision to modify EMANATE to focus on rare patient cohorts with variants with the highest probability of responding to setmelanotide. We will continue to evaluate a path to registration for the larger N221D and the POMC/PCSK1 and LEPR VUS populations. We look forward to working with our collaborators across the globe to enroll and conduct these trials, as we pursue our vision of expanding setmelanotide's reach to address the underlying cause of early-onset, severe obesity and hyperphagia in many more patients with rare genetic diseases of obesity."

Specific to the heterozygous POMC/PCSK1 and LEPR sub-studies, the variant classifications of pathogenic, likely pathogenic or suspected pathogenic within variants of uncertain significance are determined by a CLIA/CAP certified laboratory in alignment with a framework established by the American College of Medical Genetics. The Company believes patients with these variant classifications have the highest probability of response to setmelanotide based on data from the exploratory Phase 2 Basket Study.

Rhythm anticipates 12-18 months to enroll approximately 400 patients in the trial. EMANATE will enroll patients with hyperphagia and obesity that began in early childhood. In each of the four sub-studies, patients will be randomized one-to-one to daily setmelanotide or placebo. The primary efficacy endpoint in each sub-study is the mean change from baseline to 52 weeks in body weight, assessed as percent change in body mass index (BMI) in response to setmelanotide compared to placebo.

In the Phase 2 DAYBREAK trial, Rhythm modified enrollment criteria to focus initially on rare variants associated with 10 prioritized MC4R-relevant genes, which the Company and key opinion leaders believe have the highest probability of success. The Company decided to pause the enrollment of patients with variants in additional MC4R pathway genes and will evaluate expansion of DAYBREAK to these genes based on the early clinical data from the prioritized genes.

Rhythm began enrolling DAYBREAK in January 2022. DAYBREAK is a two-stage trial, beginning with a 16-week open-label stage followed, for patients who demonstrate a clinically meaningful response to setmelanotide, by a 24-week double-blind, placebo-controlled stage. The trial will now enroll approximately 100 to 200 patients with hyperphagia and severe obesity and a variant in one of 10 genes. The Company believes this two-stage design is an efficient way to assess clinically meaningful response to setmelanotide. Each genetically defined cohort can read out results independently.

The Company expects that the changes to the EMANATE and DAYBREAK trials, coupled with a streamlining of the Company's planned global network of clinical trial sites, will result in meaningful cost savings. Rhythm now expects that, as a result of these and other program changes, its existing cash, cash equivalents and short-term investments will be sufficient to fund operations into at least the fourth quarter of 2023.

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 November 2021 and is currently assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 16, 2022, for the treatment of obesity and control of hunger in adult and pediatric patients six years of age and older with Bardet-Biedl Syndrome (BBS) or Alström syndrome. A Type II variation application to the European Medicines Agency 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 also is under review. 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. 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 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 the anticipated timing for initiation of clinical trials, enrollment 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 the sufficiency of our cash, cash

equivalents and short-term investments to fund our operations. 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 Annual Report on Form 10-K for the year ended December 31, 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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