Rhythm Pharmaceuticals Announces FDA Acceptance for Filing and Priority Review of Supplemental New Drug Application for IMCIVREE® (setmelanotide) for Patients with Bardet-Biedl Syndrome and Alström Syndrome

November 15, 2021

FDA sets PDUFA goal date of March 16, 2022

BOSTON, Nov. 15, 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 that the U.S. Food and Drug Administration (FDA) has accepted for filing the company's supplemental New Drug Application (sNDA) for IMCIVREE® (setmelanotide), a melanocortin-4 receptor (MC4R) agonist, for patients with Bardet-Biedl syndrome (BBS) or Alström syndrome. The FDA granted Priority Review of the sNDA and assigned a Prescription Drug User Fee Act (PDUFA) goal date of March 16, 2022.

"The acceptance for filing of our supplemental application by the FDA marks an important step in our efforts to address the unmet needs and bring IMCIVREE to patients and families living with Bardet-Biedl syndrome and Alström syndrome," said Linda Shapiro, M.D., Ph.D., Chief Medical Officer of Rhythm Pharmaceuticals. "The FDA's decision to grant Priority Review to the application aligns with our belief in the potential of IMCIVREE to deliver clinically meaningful and statistically significant reductions in body weight and hunger for patients with BBS and Alström syndrome while also substantially improving quality of life for these patients and their families."

A Priority Review designation is granted by the FDA for the evaluation of drug applications that may offer significant improvements in the safety or effectiveness of the treatment, prevention or diagnosis of a serious disease. Under the FDA's current PDUFA review goals, for an application granted Priority Review, the FDA aims to take action on such application within six months of receipt, compared to 10 months under standard review.

About Bardet-Biedl and Alström Syndromes
BBS and Alström syndrome are ultra-rare genetic diseases that affect multiple organ systems. Clinical features of BBS may include early-onset severe obesity, hyperphagia, cognitive impairment, polydactyly, renal dysfunction, hypogonadism, and/or visual impairment. Clinical features of Alström syndrome may include early-onset severe obesity, hyperphagia, progressive visual and auditory impairment, insulin resistance and Type 2 diabetes, hyperlipidemia, progressive kidney dysfunction, cardiomyopathy, and short stature in adulthood. Hyperphagia is an insatiable hunger that is a common feature in both of these diseases and is potentially related to impaired signaling via the MC4R pathway in the hypothalamus.

Rhythm estimates that BBS affects approximately 1,500 to 2,500 people and that Alström syndrome affects approximately 500 people in the United States, with a similar prevalence estimate in Europe. Currently, there are no approved therapies targeting the MC4R pathway to address the early-onset severe obesity and hyperphagia in BBS or Alström syndrome.

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 in September 2021 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 37,500 sequencing samples -- to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic variants. 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 U.S. 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. 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 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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