Rhythm Pharmaceuticals Completes Submission of Supplemental New Drug Application to U.S. Food and Drug Administration for IMCIVREE® (setmelanotide) for the treatment of obesity and control of hunger in Bardet-Biedl and Alström Syndromes

September 20, 2021

BOSTON, Sept. 20, 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 it has completed its supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for IMCIVREE® (setmelanotide) for the treatment of obesity and control of hunger in adult and pediatric patients 6 years of age and older with Bardet-Biedl syndrome (BBS) or Alström syndrome.

"This marks a major step in our efforts to bring IMCIVREE to more patients and families living with rare genetic diseases of obesity, including BBS, which affects approximately 1,500 to 2,500 people in the United States, and Alström syndrome, which affects approximately 500 to 1,000 people worldwide," said David Meeker, M.D., Chairman, President and CEO of Rhythm. "Our application is based on data from the pivotal Phase 3 trial in which treatment with IMCIVREE produced clinically meaningful and statistically significant reductions in body weight and in the unrelenting hunger associated with these syndromes. The submission includes a series of comprehensive individual patient narratives supporting our belief that IMCIVREE has the potential to offer the first therapeutic option for the early-onset, severe obesity and unrelenting hunger that characterize these syndromes."

The FDA typically has a 60-day filing review period to determine whether the sNDA is sufficiently complete and acceptable for filing. Rhythm has requested priority review for the application, which, if granted, could provide a target FDA review period of six-months from the date the sNDA is accepted. The Company also expects to submit a Type II variation marketing authorization application (MAA) to the European Medicines Agency (EMA) in the fourth quarter of 2021, which also will cover both BBS and Alström syndrome.

As first reported in December 2020, Rhythm's Phase 3 trial of setmelanotide in patients with BBS or Alström syndrome met its primary endpoint and all key secondary endpoints, with statistically significant and clinically meaningful reductions in weight and hunger at 52 weeks on therapy. All primary endpoint responders were patients with BBS; no patients with Alström syndrome met the primary endpoint of more than 10 percent weight loss.

Dr. Meeker continued, "While there are limited data for the ultra-rare Alström syndrome population, there is clear evidence of a marked and sustained weight loss in older children and adults, and consistent reductions in BMI-Z score in younger patients. We look forward to working closely with the FDA as we pursue this additional approval."

Rhythm also announced data in April 2021 at the Pediatric Endocrine Society annual meeting from a predefined exploratory endpoint showing the impact of setmelanotide on BMI-Z scores for patients younger than 18 years old with BBS or Alström syndrome. The BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex. Setmelanotide was associated with statistically significant and clinically meaningful reductions in BMI-Z scores. For 16 patients younger than 18 years of age with BBS, the mean BMI-Z score was reduced from 3.74 at baseline to 2.98 for a reduction of -0.76, or -24.5 percent (p=0.0006).

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 cognitive impairment, polydactyly, renal dysfunction, hypogonadism, and visual impairment. Clinical features of Alström syndrome may include progressive visual and auditory impairment, insulin resistance and Type 2 diabetes, hyperlipidemia, progressive kidney dysfunction, cardiomyopathy, and short stature in adulthood. Insatiable hunger, also known as hyperphagia, and severe obesity beginning early in life may be common in people living with either BBS or Alström syndrome. In the United States, the Company estimates that BBS affects approximately 1,500 to 2,500 people and that Alström syndrome affects approximately 500 people. Currently, there are no approved therapies targeting the MC4 receptor pathway for reducing body weight and hunger 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. 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 and EC-approved 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 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 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. 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, 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.