Rhythm Pharmaceuticals Completes Submission of Type II Variation Application to the European Medicines Agency for IMCIVREE® (setmelanotide) for Bardet-Biedl and Alström Syndromes

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BOSTON, Oct. 14, 2021 (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 that it has submitted its Type II variation application to the European Medicines Agency (EMA) for IMCIVREE® (setmelanotide) 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.

“This marks an important milestone toward our goal of delivering IMCIVREE globally to patients with BBS and, ultimately, many other rare genetic diseases of obesity,” said David Meeker, M.D., Chairman, President and Chief Executive Officer of Rhythm. “IMCIVREE achieved clinically meaningful and statistically significant results in our Phase 3 trial in BBS and provided evidence of marked and sustained weight loss in patients with Alström syndrome treated in our Phase 2 and 3 trials. Based on these data, we believe IMCIVREE will be the first medicine to effectively address the severe, early-onset obesity and hyperphagia that characterize these diseases. We look forward to working closely with regulatory authorities in the European Union to deliver IMCIVREE to these additional populations.”

“The BBS community in the EU is particularly well established, with approximately 1,500 patients diagnosed and being cared for at academic centers,” said Yann Mazabraud, Executive Vice President, Head of International of Rhythm. “Importantly, many of these patients present with the severe obesity and hyperphagia that treatment with IMCIVREE is designed to address. We are eager to continue our targeted efforts to increase understanding of BBS and the potential benefits of IMCIVREE and, if authorised, look forward to bringing this treatment to market quickly as a key step toward transforming the care of people living with rare genetic diseases of obesity.”

The EMA submission is based on data from Rhythm’s pivotal Phase 3 clinical trial of setmelanotide in patients with BBS or Alström syndrome. As previously reported, the study 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 patients who met the primary endpoint defined as more than 10 percent weight loss had BBS and none had Alström syndrome. However, data from this Phase 3 trial is supported by results from the Phase 2 trial, which suggest that treatment with setmelanotide may result in decreased weight and hunger in people living Alström syndrome. In addition, data from a predefined exploratory endpoint showed that, in BBS and Alström syndrome patients younger than 18 years old, setmelanotide treatment was associated with clinically meaningful reductions in BMI-Z scores. The BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex.

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 is common in people living with either BBS or Alström syndrome. 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 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. 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. 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 deficiencies. Rhythm's headquarters is in Boston, MA.

IMCIVREE® (setmelanotide) Indication
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.

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).

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 and EU 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, 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 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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