Rhythm Pharmaceuticals Announces FDA Approval of IMCIVREE® (setmelanotide) for Use in Patients with Bardet-Biedl Syndrome

June 16, 2022

-- IMCIVREE now available for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to Bardet-Biedl syndrome --

-- First and only FDA-approved therapy that targets impairment in the MC4R pathway - a root cause of early-onset, severe obesity and hyperphagia associated with Bardet-Biedl syndrome --

-- Approval based on Phase 3 trial results that demonstrated statistically significant reductions in weight and hunger in patients with Bardet-Biedl syndrome --

-- Management to host conference call today at 5:00 p.m. ET --

BOSTON, June 16, 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 that the U.S. Food and Drug Administration (FDA) has approved the Company's supplemental New Drug Application (sNDA) for IMCIVREE® (setmelanotide), a melanocortin-4 receptor (MC4R) agonist, for patients with Bardet-Biedl syndrome (BBS).

With today's approval, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years old and older with monogenic or syndromic obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, or BBS.

"This FDA approval represents a significant milestone for Rhythm, validating our strategy of developing IMCIVREE for people with hyperphagia and severe obesity caused by rare MC4R-pathway diseases and allowing us to provide our precision therapy to an established community of patients living with BBS and their families who are eagerly awaiting a new treatment option," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "Leveraging the robust infrastructure we put in place following the initial approval of IMCIVREE for obesity due to biallelic POMC, PCSK1 or LEPR deficiency and our new high-touch patient support services to assist patients throughout the journey from diagnosis to ongoing treatment, we are able to make IMCIVREE available for BBS immediately. We look forward to delivering this important medicine to the growing community of patients and families in need of options that can effectively address the obesity and hyperphagia that affect many people living with BBS."

IMCIVREE was initially approved by the FDA in November 2020 for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency. IMCIVREE's label was updated today to include an FDA-approved test developed under a post-marketing commitment to confirm variants in *POMC*, *PCSK1* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

IMCIVREE is not indicated for the treatment of patients with obesity due to suspected POMC, PCSK1 or LEPR deficiency with *POMC*, *PCSK1* or *LEPR* variants classified as benign or likely benign, or other types of obesity not related to POMC, PCSK1 or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity.

In clinical trials, IMCIVREE was generally well-tolerated. Disturbance in sexual arousal, depression and suicidal ideation, increased skin pigmentation and darkening of pre-existing nevi, and benzyl alcohol toxicity in neonates and low birth-weight infants may occur. The most common adverse reactions were skin hyperpigmentation, injection site reactions and nausea.

BBS is a rare genetic disease that affects approximately 1,500-2,500 people in the U.S. People living with BBS may experience insatiable hunger, also known as hyperphagia, and severe obesity beginning early in life. BBS may also be associated with cognitive impairment, polydactyly, renal dysfunction, hypogonadism, and visual impairment.

Robert Haws, M.D., a BBS expert who recently retired from his role as Director of the Center of Excellence for Bardet-Biedl Syndrome at the Marshfield Clinic Research Institute in Wisconsin, said, "This approval marks an important achievement for the entire BBS community including patients and their families, clinicians and researchers, as we all have been looking forward to a therapy that addresses the burdens of hyperphagia and severe obesity that significantly affect daily lives of patients and caregivers living with BBS. IMCIVREE achieved significant reductions in weight and hunger in patients with BBS, providing this community a much needed and first-ever therapeutic option."

“It is important to understand that the early-onset, severe obesity and pathologic hunger experienced by many people living with BBS can be debilitating, especially when you consider the impact of food-seeking behavior on families,” said Timothy Ogden, President, BBS Foundation and Family Association. “Challenges in managing weight and hunger have dramatically negative effects on health, well-being, and quality of life for those living with BBS, and we are thrilled finally to have a new treatment option to address this significant unmet need.”

Data from Phase 3 trial evaluating IMCIVREE in BBS
The FDA application for IMCIVREE was based on data from Rhythm’s pivotal Phase 3 clinical trial, which was the largest and longest interventional clinical trial in BBS. In the clinical trial, IMCIVREE delivered early, significant and sustained weight reduction. The trial met its primary endpoint and all key secondary endpoints, with statistically significant reductions in weight and hunger at 52 weeks on therapy.

As presented in the label, in patients aged ≥6 years with obesity due to BBS (N=31):

- Mean percent change in BMI was -7.9% without requirements for diet and exercise;
- Placebo-adjusted change in BMI was -4.5% in a 14-week double-blind placebo-controlled stage (IMCIVREE n=22; -4.6% change in BMI; placebo n=22; -0.1% change in BMI); and
- Statistically significant mean change in hunger score was -2.1 at 52 weeks in patients 12 years and older who were able to self-report their hunger (n=14).

Rhythm also announced that the FDA issued a complete response letter for the sNDA for setmelanotide in Alström syndrome. Rhythm plans to reevaluate potential paths forward in Alström syndrome in the U.S.

“We appreciate the FDA’s careful review of our sNDA for IMCIVREE for the treatment of Alström syndrome, but are disappointed in this outcome,” added Dr. Meeker. “We are tremendously grateful to the Alström syndrome patients, caregivers and physicians who participated in our clinical development efforts and look forward to providing an update regarding our path forward.”

Rhythm InTune offers personalized support to patients, caregivers and physicians
Today, the Company also announced the launch of Rhythm InTune, a program that provides personalized support for individuals living with rare genetic diseases of obesity. Rhythm InTune provides education and resources tailored to fit each patient’s unique need, with a dedicated patient education manager as a single point of contact. Rhythm InTune is designed to provide ongoing treatment support to patients who opt in by educating patients and their health care providers, navigating insurance coverage as they start treatment, providing injection support and offering education on what to expect. For more information, contact patientsupport@rhythmtx.com.

Conference call information
Rhythm Pharmaceuticals will host a live conference call and webcast at 5:00 p.m. ET today to discuss the FDA approval of IMCIVREE for patients with BBS. The conference call may be accessed by dialing (844) 498-0570 (domestic) or (409) 983-9726 (international) and referring to conference ID 2782343. 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 Setmelanotide
Setmelanotide is a melanocortin-4 receptor (MC4R) agonist. The MC4R is part of the key biological pathway that regulates hunger, caloric intake and energy expenditure. Variants in genes may impair the function of the MC4R pathway, potentially leading to hyperphagia and early-onset, severe obesity. Rhythm is developing setmelanotide as a targeted therapy to potentially restore the function of an impaired MC4R pathway and, in so doing, potentially reduce hunger and weight in patients with rare genetic diseases of obesity.

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.

Rhythm’s Type II variation application to the European Medicines Agency (EMA) for the treatment of obesity and control of hyperphagia in adult and pediatric patients 6 years of age and older with BBS is under review. The Company is also continuing to advance the most comprehensive clinical research program ever initiated in MC4R pathway diseases, including the pivotal Phase 3 EMANATE clinical trial evaluating setmelanotide in four independent sub-studies in patients with obesity due to POMC insufficiency caused by heterozygous variants in the *POMC* or *PCSK1* genes, LEPR insufficiency caused by heterozygous variants in the *LEPR* gene, SRC1 deficiency caused by a variant in the *NCOA1* gene, and SH2B1 deficiency caused by a variant in the *SH2B1* gene or 16p11.2 deletion encompassing the *SH2B1* gene. The Phase 2 DAYBREAK trial is evaluating setmelanotide in patients with severe obesity and hyperphagia caused by rare variants associated with 10 prioritized MC4R-relevant genes. Rhythm has also initiated a Phase 3 pediatric trial and a Phase 3 trial evaluating a weekly formulation of setmelanotide.

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 monogenic or syndromic obesity due to:

- Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in *POMC*, *PCSK1* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)
- Bardet-Biedl syndrome (BBS)

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, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Depression and suicidal ideation have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Skin Pigmentation and Darkening of Pre-existing Nevi: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new 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. Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS
Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at 833-789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the full Prescribing Information for additional Important Safety Information.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. Rhythm’s precision medicine, IMCIVREE (setmelanotide), is approved 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 monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). The European Commission (EC) and Great Britain’s Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized IMCIVREE 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 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 in the 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 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.

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 with respect to our ongoing DAYBREAK, EMANATE, Phase 3 pediatric trials and Phase 3 weekly switch trials, our expectations surrounding potential regulatory submissions, approvals and timing thereof, including from the U.S. FDA

and EMA, our business strategy and plans, including regarding commercialization of IMCIVREE, 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 March 31, 2022 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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A photo accompanying this announcement is available at https://www.globenewswire.com/NewsRoom/AttachmentNg/ab80a1b3-b17d-409d-9943-2d4737f91ae7

IMCIVREE (setmelanotide) injection

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Bardet-Biedl Syndrome

Source: Rhythm Pharmaceuticals, Inc.