Rhythm Pharmaceuticals Announces FDA Approval of IMCIVREE™ (setmelanotide) as First-ever Therapy for Chronic Weight Management in Patients with Obesity Due to POMC, PCSK1 or LEPR Deficiency

November 27, 2020

-- Indicated 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 --

-- Approval supports company's approach to address rare genetic diseases of obesity associated with an impaired MC4 receptor pathway --

-- People living with these rare genetic diseases of obesity struggle with insatiable hunger and excessive weight gain beginning at a young age --

-- Approval based on data from two 52-week open-label trials that demonstrated clinically meaningful and statistically significant weight loss and reduction of hunger --

-- Rare Pediatric Disease Priority Review Voucher issued to Rhythm by FDA --

-- Company to host conference call today at 9:30 a.m. ET --

BOSTON, Nov. 27, 2020 (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, announced today that the U.S. Food & Drug Administration (FDA) has approved IMCIVREE™ (setmelanotide) 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 confirmed by genetic testing. With this approval, IMCIVREE becomes the first-ever FDA approved therapy for these rare genetic diseases of obesity.

"Our first new drug approval is a major milestone for Rhythm, and we look forward to delivering on the promise of IMCIVREE for patients suffering with obesity due to POMC, PCSK1 or LEPR deficiency," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "With IMCIVREE, we are advancing a first-in-class, precision medicine that is designed to directly address the underlying cause of obesities driven by genetic deficits in the melanocortin-4 (MC4) receptor pathway."

Obesity due to POMC, PCSK1 or LEPR deficiency are ultra-rare diseases caused by variants in *POMC, PCSK1* or *LEPR* genes that impair the MC4 receptor pathway, which is a pathway in the hypothalamus that is responsible for regulating hunger, energy expenditure and consequently body weight. People living with obesity due to POMC, PCSK1 or LEPR deficiency struggle with extreme, insatiable hunger beginning at a young age, resulting in early-onset, severe obesity. As an MC4 receptor agonist, IMCIVREE is designed to restore impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor. There have been no FDA-approved therapies specifically indicated to manage weight in obesity due to POMC, PCSK1 or LEPR deficiency prior to IMCIVREE. Rhythm expects to make IMCIVREE commercially available to patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency in the U.S. in the first quarter of 2021.

"Many patients and families who live with these diseases face an often burdensome stigma associated with severe obesity. To manage this obesity and control disruptive food-seeking behavior, caregivers often lock cabinets and refrigerators and significantly limit social activities," said Jennifer Miller, M.D., pediatric endocrinologist at University of Florida Health. "This FDA approval marks an important turning point, providing a much needed therapy and supporting the use of genetic testing to identify and properly diagnose patients with these rare genetic diseases of obesity."

The FDA approval of IMCIVREE is based on results from the largest studies conducted to date in obesity due to POMC, PCSK1 or LEPR deficiency. In Phase 3 clinical trials, 80 percent of patients with obesity due to POMC or PCSK1 deficiency achieved greater than ten percent weight loss and 45.5 percent of patients with obesity due to LEPR deficiency achieved greater than ten percent weight loss after one year of treatment with IMCIVREE.

Consistent with prior clinical study experience, IMCIVREE was generally well-tolerated in both trials. The most common adverse events were injection site reaction, skin hyperpigmentation, and nausea. Warnings and precautions include disturbance in sexual arousal, depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi. There may be a 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.

"We know that not all obesity is the same, and genetic testing plays a key role in enabling physicians, patients and families to understand the underlying cause of certain severe obesities," said Murray Stewart, M.D., Chief Medical Officer of Rhythm. "In addition to *POMC, PCSK1* and *LEPR* genes, we are continuing our efforts to identify further genes and populations to evaluate the potential for setmelanotide to address the insatiable hunger and early-onset severe obesity that characterize these diseases."

With this approval, the FDA issued a Rare Pediatric Disease Priority Review Voucher (PRV) to Rhythm. The PRV can be redeemed to receive priority review for any subsequent marketing application or sold or transferred to other companies for their programs. The FDA previously granted Breakthrough Therapy Designation to setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor pathway, as well as orphan drug designation for obesity due to POMC (including PCSK1) and LEPR deficiencies.

Rhythm's Marketing Authorization Application (MAA) for setmelanotide to treat people living with obesity due to POMC, PCSK1 or LEPR deficiency is currently under review by the European Medicines Agency (EMA). The EMA has previously granted PRIority MEdicines (PRIME) designation for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency diseases of the MC4 receptor pathway. Additionally, the Company is currently evaluating setmelanotide for reduction in hunger and body weight in a pivotal Phase 3 trial in people living with Bardet-Biedl or Alström syndrome with topline data expected late in the fourth quarter of 2020 or early in the first quarter of 2021. Rhythm also continues to enroll patients in its Phase 2 Basket Study designed to rapidly facilitate proof-of-concept in new indications.

Conference Call Information
Rhythm will host a live webcast beginning at 9:30 a.m. ET today to discuss the FDA approval of IMCIVREE. To access the live call, please dial (844) 498-0570 (domestic) or (409) 983-9726 (international) and refer to conference ID 8468472. A webcast of the conference call will be available under "Events and Presentations" in the Investors & Media section of Rhythm's website at http://ir.rhythmtx.com. The archived webcast will be available on Rhythm's website approximately two hours after the conference call and will be available for 90 days following the call.

IMCIVREE™(setmelanotide) Indication
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 for IMCIVREE.

About Rhythm Pharmaceuticals
Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic diseases of obesity. The company is advancing setmelanotide, its melanocortin-4 (MC4) receptor agonist, to treat a number of rare genetic diseases of obesity. The Company is leveraging the Rhythm Engine and the largest known obesity DNA database, now with more than 30,0000 sequencing samples from individuals with severe obesity, to improve the understanding, diagnosis and potentially the treatment of rare genetic diseases of obesity. For healthcare professionals, visit www.UNcommonObesity.com for more information. For patients and caregivers, visit www.LEADforRareObesity.com for more information. The company is based 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 the anticipated timing for release of clinical trial data and our expectations surrounding potential regulatory approvals and timing thereof, and our business strategy and plans, including regarding commercialization of setmelanotide. Statements using words 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, the impact of our management transition, 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 September 30, 2020 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.

Corporate Contact:
David Connolly
Head of Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

Investor Contact:
Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannah.deresiewicz@sternir.com

Media Contact:
Adam Daley
Berry & Company Public Relations
212-253-8881
adaley@berrypr.com

US-SET-2000083 11/2020

A photo accompanying this announcement is available at https://www.globenewswire.com/NewsRoom/AttachmentNg/c3ad0a6f-f4bf-4444-9c6d-be14f11ef6cd

Source: Rhythm Pharmaceuticals, Inc.