Rhythm Pharmaceuticals Receives Positive CHMP Opinion for Setmelanotide for Treatment of Obesity and Control of Hunger Associated with POMC, PCSK1 and LEPR Deficiency

May 21, 2021

European Commission decision anticipated in July

BOSTON, May 21, 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 the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending marketing authorization for setmelanotide for the treatment of obesity and the control of hunger associated with confirmed loss-of-function biallelic proopiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

"People living with these rare genetic diseases experience early-onset, rapid weight gain and severe, insatiable hunger, and, despite significant effort to control their weight and appetite with supportive care and lifestyle interventions, patients often regain weight after any short-term period of weight loss," said Karine Clément, M.D., Ph.D., Professor of Nutrition at Pitié-Salpêtrière Hospital, Sorbonne Université and Head of the INSERM Nutriomics Laboratory in Paris. "With this positive opinion based on data from the largest clinical trials to date in these patient populations, people living with POMC, PCSK1 or LEPR deficiency obesities in Europe may soon have a therapeutic option with the potential to reduce their hunger and body weight."

The CHMP opinion on setmelanotide, which has the PRIority MEdicines (PRIME) designation, will now be reviewed by the European Commission. A final decision on the marketing authorization application for setmelanotide is anticipated in July 2021. If approved by the European Commission, setmelanotide would be the first treatment in the EU indicated for these rare genetic diseases of obesity and would be commercialized under the brand name IMCIVREE ™.

"We are excited by this positive opinion from the CHMP, which marks a significant step toward bringing setmelanotide to patients suffering from the severe obesity and insatiable hunger associated with rare genetic diseases of obesity around the world," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "We look forward to the European Commission's decision in the coming months, as we continue to build our global infrastructure to support commercial availability and broaden our ongoing clinical development program to explore setmelanotide's potential in other rare genetic diseases of obesity."

Pivotal Trials and Data Supporting Positive Opinion
POMC, PCSK1 or LEPR deficiency obesities 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 regulates 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, setmelanotide is designed to restore impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor.

The CHMP based its positive opinion on the results from two pivotal trials in which setmelanotide achieved statistically significant and clinically meaningful weight loss and reduction in hunger in patients with POMC, including PCSK1, and LEPR deficiency obesity. Across both studies, statistically significant and clinically meaningful reductions in body mass index (BMI) for adults and BMI-Z scores, which represent the number of standard deviations from median BMI by child age and sex, were achieved. These two studies, which are the largest studies conducted in these disease states to date, were identically designed one-year, open-label studies, each with a double-blind, placebo-controlled withdrawal period. Additional supportive data were gathered in an investigator-led study and an ongoing extension study.

Pivotal Data in POMC, including PCSK1, Deficiency Obesity

- Eight of 10 patients with POMC deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over approximately one year ($p<0.0001$);
- 50 percent of patients in the trial met or exceeded a 25 percent improvement in self-reported hunger scores ($p=0.0004$);
- Mean reduction from baseline in body weight was -25.6 percent ($p<0.0001$);
- Mean reduction from baseline in most hunger rating was -27.1 percent ($p=0.0005$);
- Mean weight loss was 32 kg, or 70.5 pounds, over one year on therapy.

Pivotal Data in LEPR Deficiency Obesity

- Five of 11 patients with LEPR deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over approximately one year ($p=0.0001$);
- 73 percent of patients in the trial met or exceeded a 25 percent improvement in self-reported hunger scores ($p<0.0001$);
- Mean reduction from baseline in body weight was -12.5 percent ($p<0.0001$);
- Mean reduction from baseline in most hunger rating was -43.7 percent ($p<0.0001$);
- Mean weight loss was 16.7 kg, or 36.8 pounds, over one year on therapy.

In both studies, significant decreases in BMI were demonstrated across patients who were 6 to 17 years old at baseline (n=14). As these patients had not yet completed their growth, appropriate progression in pubertal development and increases in height were observed during the study period.

In addition, both studies included a four-week placebo withdrawal period to further illustrate the effect of treatment with setmelanotide, during which participants almost immediately gained weight and experienced an increase in hunger, reversing the downward trends in weight loss and hunger scores observed during the first 12 weeks of the treatment period.

Consistent with prior clinical experience, setmelanotide was generally well tolerated in both trials. Treatment-emergent related adverse events (AEs) included injection site reactions, nausea and vomiting, headache, and increased hyperpigmentation (darkening of the skin). There were no reports of cardiovascular AEs related to setmelanotide.

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), has been approved by theU.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. IMCIVREE is the first-ever FDA approved therapy for 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
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.

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, and our business strategy and plans, including regarding commercialization 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, 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 March 31, 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.

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

Source: Rhythm Pharmaceuticals, Inc.