Rhythm Pharmaceuticals Announces Publication of Results from Phase 3 Clinical Trial of IMCIVREE® (setmelanotide) in Bardet-Biedl Syndrome in The Lancet Diabetes and Endocrinology

November 8, 2022

-- Previously disclosed data demonstrated statistically significant and clinically meaningful reductions in weight and hunger in patients with Bardet-Biedl syndrome --

BOSTON, Nov. 08, 2022 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases, today announced that previously disclosed results from a Phase 3 clinical trial that evaluated IMCIVREE® (setmelanotide), an MC4R agonist, in patients with Bardet-Biedl syndrome (BBS) have been published in the peer-reviewed journal *The Lancet Diabetes and Endocrinology*. The trial met its primary endpoint and all key secondary endpoints, with statistically significant reductions in weight and hunger at 52 weeks on therapy.

“Hyperphagia, which is a pathological hunger, and early-onset, severe obesity place a significant burden on both patients living with BBS and their families,” said Prof. Andrea M. Haqq, M.D., Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta. “The results from this pivotal Phase 3 clinical trial – the largest and longest interventional study ever conducted in BBS – showed patients with BBS achieved clinically significant weight loss, reductions in hunger and improvements in health-related quality of life, all of which are highly meaningful to patients with BBS and their caregivers.”

Based on these pivotal Phase 3 data, IMCIVREE was approved as the first therapy for chronic weight management in adult and pediatric patients 6 years of age and older with BBS in the U.S. and European Union (EU). BBS is a rare genetic disease that affects approximately 1,500-2,500 people in the U.S. and 2,500 people in the EU and United Kingdom (UK). 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.

Rhythm’s multicenter Phase 3 trial (NCT03746522) enrolled patients ≥6 years old with obesity and BBS or Alström syndrome (N=38). Patients were randomized 1:1 to receive up to 3mg of daily subcutaneous setmelanotide or placebo in a 14-week double-blind period, followed by open-label setmelanotide for 52 weeks of treatment total. The primary endpoint was the proportion of patients ≥12 years old in the full analysis set achieving ≥10% weight reduction after 52 weeks. Hunger and safety were also assessed.

As previously disclosed, treatment with setmelanotide resulted in significant weight and hunger reductions after one year of treatment among patients with BBS. The primary endpoint was achieved by 32.3% (95% confidence interval (CI), 16.7%, 51.4%; p=0.0006) of patients ≥12 years old, all of whom were patients with BBS. None of the responders were patients with Alström syndrome.

Data highlights among patients with BBS (n=32) after 52 weeks of setmelanotide include:

- Fifteen (15) patients ≥18 years achieved a mean (SD) percent reduction in BMI of -9.1% (6.8%; 95% CI, −13.4%, −4.8%);
- Fourteen (14) patients <18 years achieved a mean (SD) change in BMI Z score of −0.8 (0.5; 95% CI, −1.0, −0.5), and 12 patients (85.7%) achieved ≥0.2-point reduction in BMI Z; and
- Fourteen (14) patients ≥12 years who reported hunger scores achieved reduction of -30.5% in maximal hunger score.

The safety profile observed in this study was consistent with that observed with setmelanotide in previous clinical trials in patients with other rare MC4R pathway diseases. Skin hyperpigmentation (n=23; 60.5%) was the most common adverse event (AE). Two patients experienced serious AEs, neither of which was considered related to setmelanotide treatment.

“With early, significant and sustained weight reduction demonstrated in our Phase 3 trial, we were able to secure approvals in the United States and European Union and deliver the first treatment for obesity in patients with BBS,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “We look forward to leveraging the publication of these trial results to drive continued momentum, as we work toward our goal of bringing a new option to people who are living with this rare genetic disease around the world, while also targeting additional rare MC4R pathway diseases with our broad ongoing clinical development program.”

About Rhythm Pharmaceuticals

Rhythm is a commercial-stage biopharmaceutical company committed to 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, 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 pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). The European Commission (EC) has authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. The UK's Medicines & Healthcare Products Regulatory Agency (MHRA) authorized setmelanotide 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. 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.

Setmelanotide Indication
In the United States, setmelanotide is indicated 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 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) or BBS.

In the European Union, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) or genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Limitations of Use
In the United States and Europe, Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide 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

Skin Monitoring: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing naevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and during treatment with setmelanotide.

Heart rate and blood pressure monitoring: Heart rate and blood pressure should be monitored as part of standard clinical practice at each medical visit (at least every 6 months) for patients treated with setmelanotide.

Prolonged penile erection: Spontaneous penile erections have been reported in clinical trials with setmelanotide. Patients who have a penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment of priapism.

Depression: In clinical trials, depression has been reported in patients treated with setmelanotide. Patients with depression should be monitored at each medical visit during treatment with setmelanotide. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.

Pediatric Population: The prescribing physician should periodically assess response to setmelanotide therapy. In growing children, the impact of weight loss on growth and maturation should be evaluated. The prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Excipients: This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Patients who are pregnant or breastfeeding should be advised of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. This medicinal product should be used with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free."

ADVERSE REACTIONS
The most frequent adverse reactions are hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache

(26%).

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no data from the use of setmelanotide in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects. As a precautionary measure, setmelanotide should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in fetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide treatment as there was no proof of teratogenicity in the nonclinical data. If a patient who is taking setmelanotide and still losing weight gets pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring for the recommended weight gain during pregnancy. The treating physician should carefully monitor weight during pregnancy in a patient taking setmelanotide.

Breast-feeding
It is unknown whether setmelanotide is excreted in human milk. A nonclinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from setmelanotide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility
No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337. See Summary of Product Characteristics' APPENDIX V for a list of European national reporting systems to communicate adverse reactions.

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

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the U.S. 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, the potential benefits of setmelanotide for patients with BBS, and 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, 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, 2022 and our other filings with the U.S. 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.