Rhythm Pharmaceuticals Convenes Inaugural International Meeting on Pathway-Related Obesity: Vision of Excellence (IMPROVE) 2022

October 12, 2022

-- Approximately 100 European health care professionals invited to discuss recent scientific developments in rare pathway-related obesities --

-- Rhythm presents analysis of Phase 2 Basket Study evaluating setmelanotide in patients with obesity and MC4R variants --

BOSTON, Oct. 12, 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 the inaugural International Meeting on Pathway-Related Obesity: Vision of Excellence (IMPROVE) 2022 in Berlin, Germany from October 12-14.

IMPROVE 2022 is a scientific meeting sponsored by Rhythm for health care professionals based in Europe. Attendees are invited to discuss and share the latest scientific developments and patient care practices related to rare pathway-related obesities, including those driven by impairments in the MC4R pathway, in which genetic deficiencies can result in hyperphagia and early onset severe obesity.

“With much research, collaboration and specialized care, we are fortunate to have a well-organized community of scientific experts who have significantly advanced the understanding and treatment of many forms of obesity,” said Peter Kühnen, M.D., Institute for Experimental Pediatric Endocrinology, Charité Universitätsmedizin Berlin, Germany, who is serving as Chair of IMPROVE 2022. “IMPROVE offers an excellent opportunity for approximately 100 attending specialists to connect with colleagues from across Europe and share ideas and best practices on how to address unmet needs in the diagnosis and treatment of people with hyperphagia and severe, early-onset obesity, and how to integrate genetic tests and therapeutics as part of routine patient care.”

Dr. Kühnen is joined by Martin Wabitsch, M.D., Head of the Division of Pediatric Endocrinology and Diabetes at Ulm University Medical Center, who is serving as Co-chair of IMPROVE 2022, and an international expert faculty that includes:

- Jesús Argente, M.D., Ph.D., Professor in the Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid
- Karine Clément, M.D., Ph.D., Professor of Nutrition at Pitié-Salpêtrière Hospital, Sorbonne Université and Head of the INSERM Nutriomics Laboratory in Paris
- Hélène Dollfus, M.D., Ph.D., Hôpitaux Universitaires de Strasbourg, France
- Sadaf Farooqi, M.D., Ph.D., Wellcome-MRC Institute of Metabolic Science at the University of Cambridge
- Antje Körner, M.D., Ph.D., University Hospital Leipzig Clinic for Children and Adolescents

Rhythm presents data on patients with identified MC4R variants in exploratory Phase 2 Basket Study

At IMPROVE 2022, Rhythm is presenting a poster titled, “Setmelanotide in Patients with Obesity Due to Certain MC4R Variants Stratified as Rescuable or Nonrescuable Based on an In Vitro Functional Assay,” which details data from Rhythm’s exploratory Phase 2 Basket Study. In this study, Rhythm used an *in vitro* assay to classify MC4R variants and stratified patients into two cohorts, one of which enrolled patients with predicted setmelanotide rescuable MC4R pathway deficiency and one of which enrolled patients with predicted nonrescuable MC4R deficiency.

Twenty-three patients with predicted rescuable MC4R deficiency and 24 patients with predicted nonrescuable MC4R deficiency were enrolled in two cohorts within Rhythm’s exploratory Basket Study and all reached three months of treatment with setmelanotide. The *in vitro* assay demonstrated limited predictive value for setmelanotide response, which was defined as ≥5% body mass index (BMI) reduction after three months treatment. Data highlights include:

- 7 of 23 patients (30.4%) with MC4R variants predicted to be rescuable achieved a ≥5% BMI reduction at Month 3 (90% confidence interval (CI), 15.3%-49.6%);
    - Most responders (6 of 16) were carriers of the p.S127L heterozygous variant in the rescuable group;
- 3 of 24 patients (12.5%) with MC4R variants predicted to be nonrescuable achieved ≥5% BMI reduction at Month 3 (90% CI, 3.5%-29.2%);
- Weight loss, as determined by percent change in BMI, tended to increase over time in patients achieving ≥5% BMI reduction at Month 3, with continued weight loss in responders in both predicted rescuable and nonrescuable groups at Month 6 and Month 9 of treatment with setmelanotide; and

- 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. No new safety findings were identified.

“These data from our exploratory Phase 2 Basket Study represent an important step toward understanding the impact that gene variants can have on MC4R pathway function and its regulation of hunger, energy expenditure and body weight,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “The results suggest that patients with certain variants of the *MC4R* gene may benefit from treatment with setmelanotide, while highlighting limitations in the predictive value of our *in vitro* assay to identify which variants should be considered rescuable or nonrescuable. We plan to continue our assessment of the genetics of the MC4R pathway and opportunities to identify patients who may benefit from setmelanotide.”

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 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.

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.

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.

Paediatric 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, including with respect to the exploratory Phase 2 Basket Study, the potential benefits of setmelanotide for patients with severe obesity due to certain genetic deficiencies, and our expectations surrounding potential regulatory submissions, approvals and timing thereof, 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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