Rhythm Pharmaceuticals Announces Completion of Screening for Enrollment in Setmelanotide Phase 3 Hypothalamic Obesity Trial and Additional Updates

January 4, 2024

-- Phase 3 hypothalamic obesity top-line data expected in 1H2025 --

-- Positive reimbursement decision achieved for IMCIVREE® (setmelanotide) to treat patients with Bardet-Biedl syndrome and POMC/LEPR deficiencies in Spain --

-- IND application for RM-718 accepted by the FDA --

BOSTON, Jan. 04, 2024 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with rare neuroendocrine diseases, today provided a business update and announced it has completed screening for enrollment in the pivotal, Phase 3 clinical trial evaluating setmelanotide in patients with acquired hypothalamic obesity.

Rhythm closed screening and anticipates overenrolling the ongoing phase 3 hypothalamic obesity trial with more than 140 patients consented and going through active screening and baseline assessments. In this trial, patients with acquired hypothalamic obesity aged 4 years or older will be randomized 2:1 to setmelanotide therapy or placebo for a total of 60 weeks, including up to eight weeks for dose titration. The Company expects to obtain top-line study results in H1 2025.

“2023 was a truly transformational year for Rhythm, as we made excellent progress with the execution of our IMCIVREE ® (setmelanotide) commercial plan while also advancing important development efforts to expand the number of patients living with hyperphagia and severe obesity that could potentially benefit from this therapy,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “We believe the rapid over enrollment in less than one year and execution of our Phase 3 hypothalamic obesity trial is a strong indicator of the unmet need for an effective therapy for patients who have no approved therapeutic options and the community’s excitement around setmelanotide’s potential to make a meaningful difference in their lives.”

Positive Reimbursement Decisions Achieved in Spain

Rhythm today also announced that federal healthcare authorities in Spain have approved reimbursement for IMCIVREE® (setmelanotide) for the treatment of obesity and control of hunger associated with Bardet-Biedl syndrome (BBS) or biallelic proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or biallelic leptin receptor (LEPR) deficiency.

“We are pleased that the Ministry of Health in Spain has recognized the treatment needs of patients with hyperphagia and early-onset obesity of BBS and POMC/LEPR deficiencies and IMCIVREE as the first and only precision medicine for patients with these diseases,” said Yann Mazabraud, Executive Vice President and Head of International at Rhythm. “We are excited to achieve access in this important market and deliver IMCIVREE to patients and families.”

BBS and POMC, PCSK1 and LEPR deficiencies are rare diseases with hallmark symptoms of hyperphagia, a pathological hunger that leads to abnormal food-seeking behaviors, and early-onset, severe obesity. BBS also is associated with cognitive impairment, polydactyly, renal dysfunction, hypogonadism, and visual impairment. POMC or LEPR deficiency are ultra-rare diseases with very few patients identified. With multiple symptoms as part of a syndrome, BBS patients, while still under-diagnosed, are more easily identified. Rhythm estimates the prevalence of BBS to be approximately 700 people in Spain with approximately 100 patients identified.

RM-718 IND Accepted by the FDA

Rhythm also announced today that the FDA accepted the Company's Investigational New Drug (IND) application for RM-718, a new, weekly treatment designed to be more targeted and potent than setmelanotide with the potential to not cause hyperpigmentation. The Company anticipates beginning Phase 1 in-human trials in the first half of 2024, including a multiple-ascending dose study in patients with hypothalamic obesity.

About Rhythm Pharmaceuticals

Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with rare neuroendocrine diseases. Rhythm’s lead asset, IMCIVREE ® (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity, is approved by the 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). Both the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) have 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. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare diseases, as well as a preclinical suite of small molecules for the treatment of congenital hyperinsulinism. 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 proopiomelanocortin (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-fetal 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 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 initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and timing thereof, including for RM-718 and setmelanotide, our business strategy and plans, including regarding commercialization of setmelanotide in the United States and Europe, the application of genetic testing and related growth potential, and expectations surrounding the potential market opportunity for our product candidates. Statements using word such as “expect”, “anticipate”, “believe”, “may”, “will”, "aim" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, risks relating to our liquidity and expenses, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks relating to product liability lawsuits, inability to maintain our collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, the impact of the COVID-19 pandemic and general economic conditions on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, failure to realize the anticipated benefits of our acquisition of Xinvento B.V. or significant integration difficulties related to the acquisition, and the other important factors discussed under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 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
Executive Director, Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
857-264-4280
dconnolly@rhythmtx.com

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

Source: Rhythm Pharmaceuticals, Inc.