Rhythm Pharmaceuticals Presents Patient-reported Experiences with Hyperphagia in Hypothalamic Obesity at ENDO 2024

June 3, 2024

- Participants from the completed Phase 2 hypothalamic obesity trial reported positive changes in sleep, energy levels during setmelanotide therapy in qualitative interviews -

- Separate analysis of patients across MC4R pathway diseases showed one year of treatment with setmelanotide improved NIH, WHO weight classifications -

- Previously reported stage one results from Phase 2 DAYBREAK trial showed potential setmelanotide efficacy in multiple MC4R pathway variants; stage two data expected in Q3 2024 -

- Preclinical data demonstrated potential of RM-718 to reduce body weight and hunger -

- Additional posters feature design of Phase 1 trial of RM-718 and real-world RESTORE study -

BOSTON, June 03, 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 announced the presentation of the first patient and caregiver reported experiences from qualitative interviews following the completion of a Phase 2 trial that evaluated treatment with setmelanotide in hypothalamic obesity (HO). These results were among six Rhythm presentations at the Endocrine Society Annual Meeting & Expo (ENDO 2024) being held June 1-4 in Boston.

“We continue to advance what we believe to be the most comprehensive clinical research program ever initiated for the treatment of hyperphagia and severe obesity associated with rare melanocortin-4 receptor (MC4R) pathway diseases,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “For the first time, we presented patient and caregiver reported results showing that setmelanotide therapy in patients with hypothalamic obesity was associated with meaningful improvements in their lives beyond clinical outcomes and reductions in body mass index (BMI).”

Christian Roth, M.D., Seattle Children’s Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington, presented, “Patient- and Caregiver-reported Experiences of Hunger, Weight and Energy in Acquired Hypothalamic Obesity Before and During Setmelanotide Therapy.” In qualitative interviews before setmelanotide therapy, five participants (three patients, two caregivers) all reported experiencing substantial weight gain, unrelenting hunger, drastically reduced energy or physical activity, and interrupted nighttime sleep, primarily due to hunger associated with acquired hypothalamic obesity. In their experiences following initiation of setmelanotide therapy, all study participants reported improved energy and ability and desire to be more active, and four of five participants reported reductions in hunger, positive changes in eating behavior and improvements in sleep.

Rhythm and its collaborators also delivered two rapid-fire oral presentations and accompanying posters at ENDO 2024:

- Dr. Roth presented results from an analysis of the clinical characteristics of 58 individuals who participated in trials of setmelanotide across MC4R pathway diseases including hypothalamic obesity, proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency obesities, or Bardet-Biedl syndrome (BBS). After one year of treatment with setmelanotide, improvements of at least one obesity class were observed across all cohorts (HO: 92%; POMC deficiency: 89%; LEPR deficiency: 36%; BBS: 42%). Patients with LEPR deficiency and BBS had more severe weight categories at baseline but still showed general improvement in weight categories after one year of treatment.
- Danica Grujic, Ph.D., Senior Director, Non-Clinical Development, Translational Research & Development, Rhythm Pharmaceuticals, presented results from a preclinical study that evaluated treatment with RM-718, a selective MC4R agonist designed to be administered weekly with potential to avoid MC1R-related hyperpigmentation, in a rodent model of obesity, hyperphagia, and insulin resistance. Treatment was well-tolerated and stable weight and food intake reductions and improved insulin sensitivity were observed after three weeks.

Rhythm and its collaborators also presented three additional posters at ENDO 2024:

- Elif Oral, M.D., Associate Professor in the Division of Metabolism, Endocrinology and Diabetes (MEND) at The University of Michigan, presented previously reported stage one results from the two-stage, double-blind, placebo-controlled DAYBREAK trial that show potential setmelanotide efficacy in individuals who carry variants in *SEMA3[A-G]*, *PLXNA[1-4]*,

PHIP, *TBX3*, *MAGEL2*, or *SIM1*. At least one patient in each of those cohorts achieved ≥10% body mass index (BMI) reduction at the end of the 16-week, open-label run-in period. Overall, 49 responders were randomized into stage two, which is a 24-week, double-blind, randomized, placebo-controlled period. Setmelanotide was well tolerated with no new safety concerns.

- Dr. Roth presented the design of Rhythm's first-in-human Phase 1 trial of once-weekly RM-718 in individuals with obesity or patients with HO.
- Caroline Huber, Director, Value & Evidence, Rhythm Pharmaceuticals, presented the design of Real-world Evidence of SeTmelanotide fOr Hyperphagia and ChRonic Weight ManagEment (RESTORE), the first study to assess the real-world effectiveness of setmelanotide to provide a greater understanding of patient outcomes, such as hyperphagia and quality of life, in a clinical practice setting.

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 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). 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 investigational MC4R agonists LB54640 and RM-718, and 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 and United Kingdom, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. In the European Union and United Kingdom, setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
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.

Contraindication
Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

WARNINGS AND PRECAUTIONS

Skin Pigmentation and Darkening of Pre-Existing Nevi: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred because of its pharmacologic effect. Full body skin examinations prior to initiation and periodically during treatment should be conducted to monitor pre-existing and new pigmentary lesions.

Heart rate and blood pressure monitoring: In Europe, 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.

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Patients who have an erection lasting longer than 4 hours should seek emergency medical attention.

Depression and Suicidal Ideation: Depression and suicidal ideation have occurred. Patients should be monitored for new onset or worsening depression or suicidal thoughts or behaviors. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue setmelanotide.

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. In Europe, the prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: Setmelanotide is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS

Lactation: Not recommended when breastfeeding.

REPORTING OF SIDE EFFECTS

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also contact Rhythm Pharmaceuticals at +1 (833) 789-6337. To report directly via the Yellow Card Scheme please do so via: www.mhra.gov.uk/yellowcard. To report directly to the FDA contact 1-800-FDA-1088 or www.fda.gov/medwatch. [See section 4.8 of the Summary of Product Characteristics for information on reporting suspected adverse reactions in Europe.]

By reporting side effects, you can help provide more information on the safety of this medicine.

Please see the Summary of Product Characteristics and 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 Company's participation in and the content of its presentations at conferences including the ENDO 2024 conference; the promise and potential impact of the Company's preclinical or clinical trial data; the initiation, timing, design, or results of any clinical trials or readouts; and the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage, including the potential for setmelanotide to treat hyperphagia and severe obesity associated with melanocortin-4 receptor (MC4R) pathway diseases and additional genetic indications, as well as improve patient and caregiver quality of life, and the potential for RM-718 to reduce body weight and hunger and treat obesity. 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 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 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, general economic conditions, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the three months ended March 31, 2024 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

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

Source: Rhythm Pharmaceuticals, Inc.