Rhythm Pharmaceuticals Announces Five New Data Presentations at ObesityWeek® 2024

November 4, 2024

-- Real-world data showed mean BMI decrease of 12.8% in adult patients with acquired hypothalamic obesity (N=8) at three months on setmelanotide therapy; mean BMI decrease of 21.3% in patients (n=5) who reached six months --

-- Greater reduction in fat mass (29.7%) versus reduction in lean muscle mass (7.7%) reported from Phase 2 trial extension in patients with acquired hypothalamic obesity (n=11) after 12 months --

-- Positive data from Phase 2 DAYBREAK stage 2 showed mean BMI reduction of 12.4% in patients with rare MC4R pathway diseases on continuous setmelanotide therapy for 40 weeks (n=32) --

-- New Phase 3 VENTURE trial data showed mean BMI reduction of 23.8% in pediatric patients aged 2 - <6 years old with BBS or POMC/LEPR Deficiency (n=8) who reached 18 months on setmelanotide therapy --

-- Analyses of 43,000 Uncovering Rare Obesity® samples shows association between certain genetic variants and hyperphagia and early-onset, severe obesity --

BOSTON, Nov. 04, 2024 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company focused on transforming the lives of patients living with rare neuroendocrine diseases, today announced the presentation of new, real-world data showing improvements in hunger scores and body mass index (BMI) reductions in adult patients in France with acquired hypothalamic obesity who were treated with setmelanotide. These results are among five Rhythm posters to be presented on November 5, 2024 at ObesityWeek® 2024 in San Antonio, TX.

“Adults living with severe obesity caused by a damage to the hypothalamic region of the brain from a tumor and/or its resection or developmental abnormalities have no approved therapeutic options to treat or manage this obesity even a decade after onset,” said author Christine Poitou, MD, PhD, Professor of Nutrition; Assistance Publique-Hôpitaux de Paris - APHP, Reference Center for Rare Diseases PRADORT, Nutrition Department, Pitié-Salpêtrière Hospital ; Sorbonne Université / INSERM, Nutrition and obesities: systemic approaches (NutriOmics) research unit, Paris. “These new, real-world data showing improvements in hunger scores and clinically meaningful reductions in BMI after three or more months of setmelanotide are encouraging because they suggest that this treatment has the potential to improve clinical outcomes in adults with acquired hypothalamic obesity.”

Analysis of Three-month Real-world Data in Adults with Hypothalamic Obesity
The analysis of real-world data included eight patients with acquired hypothalamic obesity age 18 years or older with a previous resection of a tumor in the hypothalamus. These patients were being treated with setmelanotide for three months or longer in five different hospitals in France under pre-marketing early access authorization. Mean duration between the time the patients had their tumor resected and setmelanotide treatment began was 12.1 years. Results from the analysis included:

- Mean BMI reduction from baseline:
  - 5.6% (-2.3 kg/m^2) after one month of treatment (N=8);
  - 12.8% (-5.7 kg/m^2) after three months of treatment (N=8); and
  - 21.3% (-7.6 kg/m^2) after six months of treatment (n=5);
- At three months of treatment, all patients had achieved a reduction in weight of 5% or more;
- All eight patients showed a reduction in three or more categories of hunger score (daily average hunger, daily most hunger, daily least hunger, daily morning hunger) from baseline as assessed by questionnaires; and
- No new safety signals were observed.

These real-world efficacy data were consistent with data from a Phase 2 trial that demonstrated clinically beneficial outcomes with setmelanotide treatment in patients with acquired hypothalamic obesity. Rhythm’s global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity is ongoing (NCT05774756), with top-line data expected in the first half of 2025.

Analysis of Body Composition Improvements in Phase 2 Trial of Adults with Acquired HO
In an analysis of data from a Phase 2 trial in 11 patients with acquired hypothalamic obesity resulting from a hypothalamic tumor, results showed improvements in body composition after 12 or more months of continuous setmelanotide treatment. Results included:

- Mean percent change in fat mass (-29.6%) over 12 months was greater than the change in lean muscle mass (-7.7%);
- Four (4) peripubertal male patients, ages 11 to 14 years at baseline, exhibited an increase in percent lean muscle mass despite losing fat mass, further highlighting the potential limitations of BMI as a measurement in this age group; and
- No serious AEs were reported, and no new safety concerns were observed in the long-term extension portion of the trial.

Results from Stage 2 of the Phase 2 DAYBREAK Trial
The DAYBREAK trial was the most comprehensive Phase 2 trial ever initiated in rare MC4R pathway diseases. This trial was designed to evaluate setmelanotide in patients with hyperphagia and severe obesity caused by variants in one of 31 pre-identified genes known to have strong relevance to the melanocortin-4 receptor (MC4R) pathway. Stage 1 of the trial ruled out several genes for further exploration based on patient prevalence or lack of response. The trial identified six cohorts of interest for potential setmelanotide efficacy, including: PHIP, SEMA3(A-G), SIMI1, PLXNA(1-4), MAGEL2, RPGRIP1L, TBX3. In Stage 2, 49 children and adults from these cohorts entered - and 39 of them - completed a 24-week, double-blind, randomized, placebo-controlled period. Results from stage 2 showed:

- A significantly higher proportion of patients in the setmelanotide arm achieved or maintained 5% BMI reduction from baseline through the end of Stage 2 compared with the placebo arm (84.4% vs. 29.4%, p=0.001);
- 12.4% mean percent BMI reduction was observed for all patients (n=29) on continuous setmelanotide therapy of 40 weeks;
- Change in BMI between baseline and the end of stage 2 was variable between gene cohorts, with the most consistent pattern of response seen in patients with PHIP variants. Other encouraging responses were observed from the SIM1, PLXNA(1-4), and SEMA3(A-G) genes; and
- Setmelanotide was well tolerated with no new safety concerns.

“The efficient design of the exploratory DAYBREAK trial has successfully identified multiple genes of interest initially considered to have strong or very strong relevance to the MC4R pathway that merit further investigation,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “Data from DAYBREAK provide valuable insight into the MCR4 pathway, and we will continue our work to better understand which gene variants have loss of function and maybe disease causing as opposed to those variants which are benign. This work will allow us to more accurately identify patients who may respond to MC4R agonism.”

Mean BMI Reduction of 23.3% Achieved in Pediatric Patients with BBS or POMC/LEPR Deficiency ages 2 to <6yo (n=8) at 18 months
Analysis of data from the open-label Phase 3 VENTURE trial in eight pediatric patients (2 to <6 years) with MC4R pathway-associated severe obesity (due to biallelic variants in *POMC, PCSK1,* or *LEPR* or genetically confirmed Bardet-Biedl syndrome (BBS)) who had received 18 or more months of setmelanotide treatment showed sustained, clinically meaningful reductions from baseline in all weight-related parameters with no new safety concerns. The mean percent change from baseline in BMI was -23.3% at Month 18 (n=8). The most commonly reported AEs were skin hyperpigmentation and nasopharyngitis, with no serious AEs or AEs leading to drug discontinuation.

Previously, Rhythm reported topline data from the Phase 3 VENTURE trial that showed patients between 2 and <6 years old (N=12) had achieved a BMI reduction -18.4% from baseline. Eleven patients remained on therapy past 12 months, including three patients who transitioned to commercial therapy after turning 6 years old. One patient from the initial group of 12 did not complete follow-up appointments and discontinued early in the trial.

Genetic Testing Results from more than 43,000 Samples
Results of data analyses from 43,014 genetic samples from individuals with severe obesity tested in the Uncovering Rare Obesity® (URO) program demonstrated the value of testing in the diagnosis of obesity that may be linked to an underlying genetic cause. Rhythm’s URO genetic testing panel includes 79 genes and one chromosomal region known to be associated with obesity. These results include samples from 30,012 individuals younger than 18 with a BMI >97th percentile and 13,002 adults 18 years old and older with a BMI >40 and a history of childhood obesity. The analyses of these data show:

- 7.39% of individuals had a positive result according to ACMG criteria indicating a likely pathogenic or pathogenic variant for early onset obesity or who met eligibility criteria for the EMANATE trial that included pathogenic, likely pathogenic or suspected pathogenic heterozygous variants in POMC, PCSK1 or LEPR or variants of unknown significance, likely pathogenic or pathogenic in SRC1 or SH2B1;
- Family history of genetic disease was significantly associated with a positive test result;
- Early-onset hyperphagia or obesity were more strongly associated with individuals with positive genetic findings; for individuals who tested positive for pathogenic or likely pathogenic variants as defined by the American College of Medical Genetics, the mean onset age of hyperphagia or obesity was one year earlier than those for whom there were no positive genetic findings; and
- Analysis of BBS genes demonstrate a high positivity rate for pathogenic or likely pathogenic variants in individuals of Hispanic or Latino ancestry.

These presentations from ObesityWeek® 2024 will be available on Tuesday, Nov. 5, 2024, the day of the presentations here: https://hcp.rhythmtx.com/publications-presentations/

Rhythm will host a live conference call and webcast on Tuesday, Nov. 5, 2024 at 5:00 p.m. ET to review its third quarter 2024 financial results and recent business activities. Participants may register for the conference call here.

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. The EC has also authorized setmelanotide for control of hunger and treatment of obesity in children as young as 2 years old, living with BBS or POMC, PCSK1, or LEPR deficiency. 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, 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 2 years of age and above. In Europe, 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.
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 section 4.8 of the Summary of Product Characteristics for information on reporting suspected adverse reactions in Europe.

Please see the full U.S. Prescribing Information and EU Summary of Product Characteristics 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, potential regulatory submissions, approvals and timing thereof of setmelanotide and other product candidates; the timing of results from our global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity; 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 benefits of setmelanotide for patients with acquired hypothalamic obesity, POMC, PCSK1, or LEPR variants or genetically confirmed Bardet-Biedl syndrome (BBS); expectations surrounding potential clinical trial results, regulatory submissions and approvals; and the timing of any of the foregoing . 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, 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 ability to successfully commercialize setmelanotide, our liquidity and expenses, our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel, and general economic conditions, and the other important factors discussed under the caption "Risk Factors" in Rhythm's Quarterly Report on Form 10-Q for the three months ended June 30, 2024 and 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.

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Source: Rhythm Pharmaceuticals, Inc.