Rhythm Pharmaceuticals Announces 11 Presentations at The Obesity Society's Annual Meeting at ObesityWeek®

November 3, 2022

-- Analyses of Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) in children with BBS showed a significant positive correlation between degree of hyperphagia and body mass index (BMI) --

-- 84% of patients with BBS in Phase 3 clinical trial showed clinical benefit of improvement in one measure or more of weight, hunger, or QoL following setmelanotide treatment --

-- Additional presentations include updates from the Uncovering Rare Obesity® diagnostic genetic testing program and long-term data with setmelanotide in obesity due to POMC or LEPR deficiency --

BOSTON, Nov. 03, 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 a total of 11 presentations at The Obesity Society's Annual Meeting at ObesityWeek ® being held November 1-4, 2022 in San Diego.

"We are excited to deliver multiple meaningful presentations this week, highlighting our ongoing efforts to improve the recognition, diagnosis and, potentially, treatment of hyperphagia and severe obesity caused by rare MC4R pathway diseases," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "We are particularly eager to share data from new analyses of the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS), which demonstrate the penetrance and impact of obesity and hyperphagia on the Bardet-Biedl syndrome (BBS) community and underscore the significant need for a new therapeutic to address both weight and hunger. To that end, we are also pleased to share new data illustrating the potential of setmelanotide to address the root cause of rare MC4R pathway-related diseases, including BBS and hypothalamic obesity. Taken together, these presentations reflect our progress toward changing the treatment paradigm and, ultimately, improving the lives of patients with hyperphagia and severe obesity."

Results from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS)

CRIBBS is an international registry of patients with BBS that launched in 2014. At ObesityWeek®, Rhythm collaborated with the Marshfield Clinic Research Institute on multiple analyses of deidentified CRIBBS data. In one analysis, the results demonstrate that children with BBS experience high disease burden due to hyperphagia and that the severity of hyperphagia was positively correlated with higher body mass index (BMI) weight categories. In a second analysis, obesity was found to be highly prevalent in a large sample of children with BBS, and most children who had obesity continued to have it or experienced worsening weight gain over time.

In a poster titled, "Substantial Burden Associated With Hyperphagia and Obesity in Children With Bardet-Biedl Syndrome," researchers led by Jeremy Pomeroy Ph.D., M.S., Associate Research Scientist at the Marshfield Clinic Research Institute, assessed mean and median hyperphagia scores by weight category and evaluated the correlation between hyperphagia score and BMI percentile for 39 children with BBS who completed the Hyperphagia Questionnaire with scores that range from 11 to 55, with higher values indicating more significant hyperphagia. Highlights include:

- The overall mean hyperphagia score was 23.9 (median 25; range, 16 to 30);
- The mean [median] hyperphagia score increased by weight category, from 15.0 [15] among children with normal weight/underweight, to 22.8 [24] among children designated as overweight, and to 25.6 [26] among children with obesity (n = 5, 5, and 29, respectively); and
- The hyperphagia score and BMI percentile were positively and significantly correlated (Pearson r=0.32; P=0.04).

An additional poster presented by Dr. Pomeroy, titled, "Natural History of Weight Gain in Children With Bardet-Biedl Syndrome: Results From the Clinical Registry Investigating Bardet-Biedl Syndrome," includes analyses of data from 331 children aged 3 to 17 years with BBS were designed to improve understanding of weight gain patterns. Researchers assessed anthropometric measures such as BMI and self-reported use of weight-loss medications or diets. Obesity status was assessed by the percentage of the 95th percentile for BMI and classified on severity accordingly. Among children with any baseline obesity, 186 children reported two or more weight measurements more than two years apart and were included in a natural history subset. Highlights include:

- At the first CRIBBS assessment (baseline), 9% of children were classified as overweight and 81% were classified as obese

(class I, II, III: 26%, 24%, 31%);
- 29% (n=54) of children included in the natural history subset (n=186) had class III obesity at baseline;
- Overall, 67.5% (n=102) of children with obesity at baseline remained in the same or moved to a higher obesity class by the last assessment ≥2 years later; and
- In the full analysis population (n=331) and natural history subset (n=186), 22.7% (n=75) and 32.3% (n=60) of children with obesity reported using weight loss interventions, respectively, with the majority experiencing additional weight gain.

"Although patients with BBS experience significant overall disease burden, the specific relationship between hyperphagia and body weight in patients with BBS has not been fully understood," said Dr. Pomeroy. "CRIBBS is a substantial registry with an unprecedented amount of data on the natural history of this rare disease that is helping us better support patients around the world. This research presented at ObesityWeek® provides further evidence of the relationship between hyperphagia and the severity of early-onset obesity in children with BBS and suggests that treatments for weight management also need to address the root cause of hyperphagia."

Clinical benefit of treatment with setmelanotide in BBS Phase 3 clinical trial

Researchers led by Andrea M. Haqq, M.D., MHS, Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada, investigated the impact of setmelanotide across weight, hunger, and quality of life (QOL) in patients aged 6 years and older with BBS and obesity who participated in Rhythm's Phase 3 clinical trial. Additionally, stabilization of weight-related parameters and adverse events (AEs) were assessed. Their findings were presented in a poster titled, "Exploration of Clinical Improvements Following Setmelanotide Treatment in Patients With Bardet-Biedl Syndrome."

Clinical improvements were defined as ≥5% reduction in body weight for adults; ≥0.2-point decrease in BMI Z score or ≥5-point decrease in percent of the 95th BMI percentile for pediatric patients; ≥25% decrease in hunger score; increase in Impact of Weight on Quality of Life-Lite (IWQOL-Lite) score of 7.7-12; and increase in Pediatric Quality of Life Inventory (PedsQL) score of >4.4. Highlights include:

- 27 of 32 patients (84%) had clinical improvements that met thresholds in ≥1 measure at the last study visit;
- 30 of 32 patients (94%) experienced clinical improvement or weight stabilization;
- 10 of 11 evaluable patients (90.9%) experienced ≥1-point reduction in maximal hunger score;
- 18 of 19 evaluable patients (94.7%) experienced a meaningful or positive nonmeaningful (no change from baseline) improvement in QOL; and
- Setmelanotide was observed to be generally well tolerated; 1 patient discontinued study drug during placebo treatment due to an AE.

Additional ObesityWeek® presentations

In addition, Rhythm and its collaborators presented the following during ObesityWeek®:

- "Efficacy and Safety Analysis of Setmelanotide As a Novel Treatment for Hypothalamic Obesity," a poster presented by Christian Roth, M.D., Seattle Children's Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington (see details in the Rhythm press release here);
- "Weight Outcomes with Setmelanotide Over 3 Years in Patients with POMC or LEPR Deficiency Obesity," an oral presentation by Sonali Malhotra, M.D., Medical Director, Medical Affairs at Rhythm;
- "Effect of Long-term Body Composition in Patients with POMC or LEPR Deficiency Obesity Following Setmelanotide," a poster presentation by Dr. Malhotra;
- "Variants in obesity-related genes in a population with early-onset obesity," a poster presentation by Patrick Kleyn, Ph.D., Senior Vice President, Head of Translational Research and Development at Rhythm;
- "Uncovering Rare Obesity Genetic Testing Program: Utility of Genetic Testing in Adults with Obesity," a poster presentation by Dr. Kleyn;
- "Frequency of BBS and AS gene variants in a cohort with early-onset obesity," a poster presentation by Dr. Kleyn;
- "Frequency of MC4R Pathway Variants in a Large U.S. Cohort of Patients With Severe Obesity," a poster presentation by Dr. Kleyn; and
- "Clinical Benefit of Setmelanotide in Patients with Alström Syndrome," a poster presentation by Dr. Haqq.

Rhythm will make the ObesityWeek® posters and presentations available under the publications section of the company website.

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 hypothalamic obesity or BBS, and our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans and our participation in upcoming events and presentations, 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.