Rhythm Pharmaceuticals Presents New Data from Phase 3 Trial Evaluating Setmelanotide in Patients with Bardet-Biedl Syndrome (BBS) at the Pediatric Endocrine Society (PES) 2022 Virtual Annual Meeting

May 2, 2022

-- New data show setmelanotide treatment led to clinically meaningful improvements in lipid parameters, without affecting blood pressure or heart rate in patients with BBS --

-- Additional posters include data from pediatric and adolescent patients enrolled in Phase 3 trial in BBS and qualitative data regarding the impact of hyperphagia on BBS patients and their caregivers --

-- Also presenting cumulative safety data demonstrating setmelanotide was generally safe and well tolerated across 561 patients treated in overall clinical development program --

BOSTON, May 02, 2022 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a commercial-stage biopharmaceutical company committed to transforming the care of people living with rare genetic diseases of obesity, today announced the presentation of new data supporting the potential for setmelanotide to treat the early-onset obesity, hyperphagia and metabolic impairment associated with Bardet-Biedl syndrome (BBS). In addition, the Company announced cumulative safety data from across the setmelanotide clinical development program. These data were presented at the Pediatric Endocrine Society (PES) 2022 Virtual Annual Meeting, held April 28 – May 1.

The Company and its collaborators delivered one oral presentation and three e-poster presentations, including:

- New data from the 52-week Phase 3 trial evaluating setmelanotide in patients with BBS, which demonstrate that setmelanotide improved body weight measures, as well as total HDL and LDL cholesterol and triglyceride levels, with no changes in blood pressure or heart rate;
- New data from the 52-week Phase 3 trial specific to adolescents and children with BBS, which show that setmelanotide treatment was associated with clinically meaningful reductions in body mass index (BMI), BMI-Z scores, and percent of the 95th BMI percentile (%BMI$_{95}$);
- New results from a study based on in-depth interviews conducted with BBS patients and caregivers enrolled in either Rhythm's Phase 2 Basket Trial or Phase 3 BBS pivotal trial, which suggest that setmelanotide treatment reduced patients' hyperphagia, body weight, and obsessive focus on food, resulting in substantially improved general health and emotional well-being; and
- Cumulative safety data from across 561 participants treated in Rhythm's 16 Phase 1, 2, or 3 clinical trials of setmelanotide in healthy volunteers and people with obesity due to rare genetic variants, which demonstrate that setmelanotide was generally well tolerated.

"The new data presented at PES reinforce setmelanotide's potential to be a safe and effective precision therapy, which can deliver meaningful benefit to people living with BBS, reducing hyperphagia, weight, and comorbid factors of the metabolic syndrome, while also improving emotional well-being," said Linda Shapiro, M.D., Ph.D., Chief Medical Officer of Rhythm. "As we prepare for a potential U.S. approval in BBS later this quarter, we are encouraged by these new data and look forward to sharing them with the health care community, as we continue efforts to educate about BBS, the patient and caregiver experience, and the need for treatment."

New Data on the Impact of Setmelanotide Treatment on Lipid Parameters and Vital Signs from the Phase 3 Trial in BBS
Andrea Haqq, M.D., M.H.S., Professor, Department of Pediatrics, Division of Pediatric Endocrinology/Metabolism at the University of Alberta, delivered an oral presentation entitled, "Impact of Setmelanotide Treatment on Lipid Parameters and Vital Signs in Patients with Bardet-Biedl Syndrome in a Phase 3 Trial."

"Due to their early-onset, severe obesity and hyperphagia, people living with BBS are at a high risk of comorbid metabolic syndrome," said Dr. Haqq. "The data presented at PES suggest for the first time that the benefits of setmelanotide treatment go beyond weight and hunger reduction, affecting lipid parameters that are known to play important roles in increasing the likelihood that patients develop ischemic heart disease, stroke, and chronic kidney disease. These results highlight the potential for setmelanotide to address the major health ramifications associated with rare genetic diseases of obesity, and further support its advancement as a precision therapy for BBS."

The pivotal Phase 3 trial included 31 response-evaluable patients aged 7 years old or older with BBS. Patients' fasting lipid

profiles were assessed before study initiation and after 52 weeks of therapy; weight and vital signs were assessed throughout the trial. As previously disclosed, data from this Phase 3 trial show that treatment with setmelanotide was associated with significant reductions in body weight and hunger.

This presentation included new data specific to patients' lipid parameters and vital signs. Following one year of setmelanotide treatment, the mean percent changes in total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were -6.1%, 5.3%, -7.8% and -9.6%, respectively. No systematic changes in blood pressure or heart rate were identified.

New Data for Setmelanotide in Pediatric and Adolescent Patients with BBS and Severe Obesity
Robert Haws, M.D., Marshfield Clinic Research Institute, presented an e-poster entitled, "Setmelanotide Treatment in Pediatric and Adolescent Patients with Bardet-Biedl Syndrome and Severe Obesity," which provided additional data specific to adolescents and children enrolled in Rhythm's Phase 3 clinical trial. As previously disclosed, patients younger than 18 years of age with BBS (n=16) had a mean reduction in BMI-Z score of 0.8.

This presentation included new data specific to patients' BMI and %BMI $_{95}$, which show that pediatric patients with BBS had a mean reduction in BMI of -3.36kg/m^2 (-9.50%) and a mean change in %BMI$_{95}$ of -17.3.

New Data Detailing Patient- and Caregiver-reported Experience of Hyperphagia from Phase 3 Trial in BBS
In an e-poster entitled, "Patient and Caregiver-Reported Experiences of Hyperphagia in Bardet-Biedl Syndrome Before and During Setmelanotide Treatment," Claire Ervin, M.P.H., Senior Director, Patient-Centered Outcomes Assessment at RTI Health Solutions, presented qualitative data from 19 interviews conducted with BBS patients and caregivers who participated in Rhythm's Phase 2 Basket Trial and Phase 3 BBS pivotal trial.

Prior to setmelanotide treatment, all participants described their hunger, or their child's hunger, as all-consuming, and noted a negative impact on daily life, including difficulties with concentration, decrements in emotional and physical well-being and impaired relationships. All participants experienced or observed notable reductions in hunger during treatment with setmelanotide. This led to a decrease in food-seeking behaviors, weight loss, and better health. All participants reported improvements in how they felt – physically and/or emotionally – and generally reported high levels of satisfaction with treatment.

Clinical Safety Summary of Setmelanotide in Healthy Volunteers with Obesity and Patients with Rare Genetic Diseases of Obesity
Jesús Argente, M.D., Ph.D., Professor in the Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid in Spain, presented an e-poster entitled, "Clinical Safety Summary of Setmelanotide in Healthy Volunteers with Obesity and Patients with Rare Genetic Diseases of Obesity," which detailed safety data from across 16 Phase 1, 2 or 3 clinical trials of setmelanotide.

As of March 8, 2021, 561 people, including 228 otherwise healthy volunteers with obesity and 308 patients with rare genetic diseases of obesity, had received at least one dose of setmelanotide, with 24% of patients receiving treatment for at least six months and 17% of patients for one year. Data suggest that setmelanotide was generally well tolerated, with a mostly consistent safety profile across age, sex, ethnicity, race, and clinical diagnosis.

All Rhythm's presentations from PES will be available on the Publications and Presentations section of its website: https://www.rhythmtx.com/publications/

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. Rhythm's precision medicine, IMCIVREE (setmelanotide), was approved in November 2020 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 obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing and in July and September 2021, respectively, by the European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) 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. IMCIVREE is the first-ever FDA-approved and EC- and MHRA-authorized therapy for patients with these rare genetic diseases of obesity. The Company submitted a supplemental New Drug Application (sNDA) to the FDA, which was accepted for filing in November 2021 and is currently assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 16, 2022, for the treatment of obesity and control of hunger in adult and pediatric patients six years of age and older with Bardet-Biedl Syndrome (BBS) or Alström syndrome. A Type II variation application to the European Medicines Agency seeking regulatory approval and authorization for setmelanotide to treat obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS also is under review. 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.

IMCIVREE® (setmelanotide) Indication
In the United States, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. The condition must be confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes

that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the EU and Great Britain, IMCIVREE is indicated 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. IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Important Safety Information

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with IMCIVREE. Instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Monitor patients for new onset or worsening of depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

Skin Pigmentation and Darkening of Pre-Existing Nevi: IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect. This effect is reversible upon discontinuation of the drug. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions.

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS
Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Treatment with IMCIVREE is not recommended for use while 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 Full Prescribing Information, EU SmPC and MHRA SmPC for IMCIVREE.

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, our business strategy and plans, including regarding commercialization of setmelanotide, and our participation in upcoming events and presentations. 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, the impact of our management transition, 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 Annual Report on Form 10-K for the year ended December 31, 2021 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.

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