Rhythm Pharmaceuticals Presents New Data on Experience of People Living with Rare Genetic Diseases of Obesity and Provides Updates on Uncovering Rare Obesity® Genetic Testing Program

October 14, 2021

-- New data in patients with POMC or LEPR deficiency obesity show setmelanotide led to clinically meaningful improvements in health related quality of life measures and hunger --

-- Updated results from Uncovering Rare Obesity® testing program suggest up to 64.5 percent of individuals with early-onset, severe obesity may carry variants linked to rare genetic diseases of obesity --

-- Additional posters include encore presentations of data from Phase 3 trial evaluating setmelanotide in BBS and Phase 2 trial in HET obesity, as well as Phase 1b trial evaluating once-weekly setmelanotide --

BOSTON, Oct. 14, 2021 (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 presented the first-ever data on the health related quality of life (HRQOL) and experience of patients with obesity due to POMC or LEPR deficiency and updated results from the Uncovering Rare Obesity® (URO) genetic testing program at the Obesity Medicine Association's Overcoming Obesity 2021 Conference and its Digital Experience (DX) Oct. 14-23.

The Company and its collaborators delivered four poster presentations, including:

- New HRQOL data from post-hoc analyses of Phase 3 trials evaluating setmelanotide in patients with POMC or LEPR deficiency obesity that showed setmelanotide treatment led to sustained, clinically meaningful HRQOL improvements in a majority of patients;
- New results from a study based on in-depth patient interviews conducted in patients with POMC and LEPR deficiency obesity enrolled in Rhythm's pivotal Phase 3 trials, which highlighted that the reduced hunger and improved satiety resulting from setmelanotide treatment substantially and meaningfully changed patients' lives; and
- Two presentations detailing updated results from Rhythm's URO genetic testing of approximately 8,500 people in the United States with early-onset, severe obesity project that:
    - 64.5% of individuals who had genetic sequencing performed may carry variants associated with rare genetic diseases of obesity, including 54.6% with variants in the melanocortin-4 receptor (MC4R) pathway that may qualify them for enrollment in Rhythm's EMANATE or DAYBREAK trials or for treatment with IMCIVREE; and
    - 1.96% of individuals who had genetic sequencing performed may carry biallelic variants in one of 22 Bardet-Biedl Syndrome (BBS)-associated genes or the *ALMS1* gene, of which up to 0.34% carried variants considered pathogenic or likely pathogenic.

"These new data contribute to the growing body of evidence that supports setmelanotide's potential to deliver clinically meaningful weight loss and clinically meaningful improvements in patient reported hyperphagia, as well as HRQOL, reinforcing the value of setmelanotide's potential for the treatment of rare genetic diseases of obesity of the MC4R pathway," said Linda Shapiro, M.D., Ph.D., Chief Medical Officer of Rhythm. "As we prepare to initiate our next wave of clinical trials, we are encouraged by these new results from the URO genetic testing program, which suggest the potential prevalence of genetic variants among people living with early-onset, severe obesity. These results reinforce the importance of genetic testing for clinical decision making in individuals with early-onset, severe obesity and hyperphagia and support our plans to initiate the Phase 3 EMANATE and Phase 2 DAYBREAK trials later this year, which will expand our clinical development of setmelanotide into patients with variants in any of 36 genes that may impair the MC4R pathway."

New HRQOL Data and Patient-reported Experience of Hunger from Phase 3 Trials in POMC and LEPR Deficiency Obesities

Investigators presented two posters with data generated from post-hoc analyses of the Company's Phase 3 trials in POMC and LEPR deficiency obesities.

In a presentation entitled, "Quality of Life in POMC or LEPR Deficiency: Setmelanotide Phase 3 Trials," Peter Kühnen, M.D., Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin und Humboldt-Universität zu Berlin, Institute for Experimental Pediatric Endocrinology presented data on the HRQOL burden improvements before and after treatment with setmelanotide.[1] Highlights include:

- Setmelanotide resulted in clinically meaningful improvement in HRQOL in eight of 13 (73%) of patients after 52 weeks of

treatment, with improvements in HRQOL that were 2 to 3 times larger than the relevant meaningful threshold; and
- Meaningful HRQOL improvements were observed as early as Week 5 on therapy, and these improvements were maintained throughout the study as they mirrored clinically meaningful hunger reductions and weight loss in these patients.

Martin Wabitsch, M.D. Division of Pediatric Endocrinology and Diabetes, Center for Rare Endocrine Diseases, Department of Pediatrics and Adolescent Medicine, University of Ulm, Ulm, Germany, presented qualitative data from a series of patient interviews in a poster entitled, "Patient Experience of Hunger in POMC or LEPR Deficiency." Patients reported that hyperphagia and the constant inability to feel satiety negatively affects their HRQOL, while reduced hunger and improved satiety achieved on setmelanotide therapy substantially and meaningfully changed their lives, profoundly improving their ability to function at school or work. Additionally, these patients reported that discontinuing treatment with setmelanotide would be devastating.

"The results of these studies underscore the tremendous burden of POMC and LEPR deficiency obesity, better characterizing the experience of people living with these conditions and highlighting the significant impact of severe obesity and insatiable hunger on their daily lives," said Dr. Kühnen. "Importantly, these data suggest setmelanotide can deliver clinically meaningful HRQOL benefits, reducing the significant burden of disease by providing patients with improvements in their feelings of insatiable hunger, in addition to substantial weight loss. These results further reinforce the value of setmelanotide as the first U.S., EU and UK-approved precision medicine for chronic weight management in POMC and LEPR deficiency obesities."

Updated Data from the URO Testing Program
Ida Moeller, ScD, ScM, MMSc, Director of Biomedical Informatics at Rhythm, presented, "Variants in Obesity-related Genes in a Population with Early-onset Obesity." Rhythm's URO testing program is designed to expand access to genetic testing for patients with suspected rare genetic diseases of obesity in the U.S. As of July 12, 2021, Rhythm had collected genetic sequences from approximately 8,500 individuals with early-onset, severe obesity, including 788 individuals who had genetic sequencing performed on the Company's updated genetic panel with 79 genes and the full chromosomal region 16p11.2.

Based on an integrated yield weighted by the number of individuals sequenced for each gene, utilizing the data from the two panels (the original panel and the updated expanded panel), Rhythm projects that 64.5% of individuals sequenced may carry actionable variants linked to rare genetic diseases of obesity.[2] Rhythm also estimates that 54.6% of individuals sequenced carry variants in the MC4R pathway that may qualify them for enrollment in Rhythm's EMANATE or DAYBREAK trials or commercial treatment with IMCIVREE.

Additionally, Dr. Robert Haws, M.D., Marshfield Clinical Research Institute, presented, "Frequency of BBS and ALMS1 Variants in a Cohort With Early-onset Obesity." Based on updated URO results, the Company projects that 0.34% of individuals with early-onset, severe obesity may carry pathogenic or likely pathogenic variants in genes known to be associated with BBS or Alstrom syndrome (or 0.24%, excluding patient samples from a leading BBS clinic where higher frequency of BBS-related variants would expected). Including patients with variants of unknown significance (VUS), Rhythm estimates that 1.96% of individuals with early-onset, severe obesity may carry biallelic variants in one of 22 known BBS-associated genes or *ALMS1*.[3]

Also at the Overcoming Obesity 2021 Conference, Rhythm and its collaborators presented three additional abstracts as posters, all of which detailed previously reported clinical data:

- "Efficacy and Safety of the Melanocortin-4 Receptor Agonist Setmelanotide in Obesity Due to Bardet-Biedl Syndrome: a Phase 3 Trial," as presented by Dr. Robert Haws, M.D., Marshfield Clinical Research Institute;
- "Setmelanotide in POMC, PCSK1, or LEPR Heterozygous Deficiency Obesity (Phase 2)," as presented by Sadaf Farooqi, Ph.D., Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge;
- "Trial of a Once-Weekly Setmelanotide Formulation in Patients with Obesity," as presented by Annette Valles-Sukkar, Director Clinical Operations, Rhythm Pharmaceuticals.

All Rhythm's presentations from Obesity Medicine Association's Overcoming Obesity 2021 Conference and its Digital Experience will be available on the Publication 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. 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 37,500 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, 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, 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 quarterly period ended June 30, 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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[1] Assessments were taken for patients in Rhythm's Phase 3 trials who experienced weight loss of at least five kilograms (or at least five percent of baseline body weight for the patients who weighed less than 100 kg). QOL was assessed using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) scale for patients 18 years or older, and using the Pediatric Quality of Life Inventory (PedsQL) for children and adolescents aged 8 to 12 and 13 to 17 years, respectively.

[2] The 64.5% figure represents a weighted yield from 8,599 URO samples collected as of July 12, 2021. Prior to May 2021, Rhythm's URO panel tested for variants in 40 obesity-related genes, including 11 genes eligible for the DAYBREAK or EMANATE trials; data for those 11 genes is available in all 8,599 samples. Rhythm launched URO 2.1/3.0 in early May 2021, which now sequences 79 obesity-related genes and the 16p11.2 chromosomal region, including 25 additional DAYBREAK/EMANATE genes. Data on all 79 genes (including all 36 DAYBREAK/EMANATE genes) was available for 788 patients, and then used to calculate a weighted yield across the total study population.

[3] Data on the frequency of *BBS* and *ALMS1* variants were collected from URO samples as of July 5, 2021, which included a smaller sample size of 8,459 sequenced individuals.

Source: Rhythm Pharmaceuticals, Inc.