Rhythm Pharmaceuticals Presents New Data from Phase 2 Basket Study Showing Continued Weight Loss at Up to Nine Months in Patients with HET Obesity on Setmelanotide at ENDO 2021

March 20, 2021

-- Responders with HET obesity achieved mean weight loss of greater than 12 percent at nine months on setmelanotide therapy --

-- Additional poster presentations include Phase 3 data in Bardet-Biedl and Alström syndromes and analyses of adverse events in Phase 2 and Phase 3 studies in POMC, PCSK1, or LEPR deficiency showing consistent safety results for setmelanotide --

BOSTON, March 20, 2021 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic diseases of obesity, today announced that three late-breaking data presentations from Phase 2 and Phase 3 studies of setmelanotide were presented during the 103rd Annual Meeting and Expo of the Endocrine Society (ENDO 2021) held virtually March 20-23.

Sadaf Farooqi, M.D., Ph.D., University of Cambridge, UK, presented proof-of-concept data from Rhythm's Phase 2 study evaluating setmelanotide in individuals living with heterozygous (HET) obesity due to genetic variants in one of two alleles of the *POMC*, *PCSK1* or *LEPR* gene. The oral presentation included new weight loss data that showed patients with HET obesity who were classified as setmelanotide-responsive at three months continued to lose weight as they remained on treatment, with a mean weight loss of 12.3 percent at nine months on therapy.

In addition, two on-demand posters on setmelanotide were presented. Topline data from Rhythm's Phase 3 trial evaluating setmelanotide in patients with Bardet-Biedl syndrome (BBS) or Alström syndrome were presented by Robert Haws, M.D., of the Marshfield Clinic Research Institute. Also, Karine Clément, M.D., Ph.D., of Pitié-Salpêtrière Hospital in Paris, presented safety data from three trials evaluating setmelanotide in a total of 35 patients with severe obesity due to leptin receptor (LEPR), proopiomelanocortin (POMC), or proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency.

"We are pleased to have world-renown physicians and scientists present these data that we believe support setmelanotide's potential as a targeted therapy to treat genetically defined patients with early-onset, severe obesity and hyperphagia. In particular, these new data in HET obesity patients demonstrate the potential for deeper, durable responses with continued therapy," said Murray Stewart, M.D., Chief Medical Officer of Rhythm. "These data give us further confidence as we advance setmelanotide through a multi-faceted clinical development program designed to address a range of rare genetic diseases of obesity caused by defects within the melanocortin-4 receptor (MC4R) pathway."

Effects of setmelanotide observed in patients with HET obesity
Dr. Farooqi, professor at the Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre delivered an oral presentation entitled, "Effects of Setmelanotide in in Patients with POMC, PCSK1 or LEPR Heterozygous Deficiency Obesity in a Phase 2 Study."

"Patients with heterozygous mutations in *POMC, PCSK1* or *LEPR* genes that impair the MC4R pathway can suffer from severe obesity and hyperphagia, which cannot be controlled by existing therapeutic interventions, diet or exercise," Dr. Farooqi said. "These data, showing that treatment with setmelanotide achieved clinically meaningful weight loss at three months that was sustained and deepened at nine months, are quite encouraging, particularly in this refractory patient population. I look forward to learning more about the genetic causes of obesities and about setmelanotide as it is advanced into additional pivotal Phase 3 studies."

The open-label, single-arm Phase 2 study included patients 6 years old or older with HET obesity. Participants received once daily setmelanotide at the therapeutic dose for 12 weeks. A total of 35 patients, whose mean baseline BMI was 50.3 kg/m^2, were included in the analysis, which was previously reported by Rhythm in January 2021. The primary endpoint was mean percent change from baseline in body weight, and 34.3 percent of all patients in the study (12/35) responded with 5 percent or greater weight loss at three months. Mean weight loss among responders was -10.1 percent at three months.

New data presented at ENDO 2021 included an analysis that showed that, among people who responded to treatment with setmelanotide at three months, response was maintained for up to nine months (n=9) with a mean percent change in body weight from baseline of -12.3 percent (90% CI, -16.3% to -8.4%), as of Feb. 23, 2021.

The adverse event (AE) profile for setmelanotide continued to be consistent with what has been previously reported including skin hyperpigmentation, nausea, and injection site pruritis.

Topline data from Phase 3 trial in Bardet-Biedl and Alström syndromes
Dr. Haws, director of the Clinical Research Center at the Marshfield Clinic Research Institute in Marshfield, Wisc., presented a poster entitled, "A Phase 3 Trial in Participants with Obesity Due to Bardet-Biedl Syndrome or Alström Syndrome: Efficacy and Safety of the Melanocortin 4 Receptor Agonist Setmelanotide."

As previously disclosed, data from this Phase 3 trial showed that treatment with setmelanotide was associated with significant body weight and hunger reduction in obesity due to BBS or Alström syndrome. The study met its primary and all key secondary endpoints, demonstrating statistically significant and clinically meaningful reductions in weight and hunger scores, with patients with BBS comprising all primary endpoint responders. No patients with Alström syndrome met the primary endpoint. The study included 31 patients 12 years old or older who were evaluable for the primary endpoint,

including 28 patients with BBS and three patients with Alström syndrome.

This presentation included new weight-loss data specific to adults that showed that patients 18 years old and older with BBS (n=15) had a mean weight loss from baseline of 9.4 percent. Additionally, the presentation included previously disclosed data specific to adolescents and children, which showed that patients younger than 18 years of age with BBS (n=16) had a mean reduction in BMI-Z scores of 0.8. The BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex.

Setmelanotide safety results from Phase 2 and Phase 3 studies in obesity due to POMC, PCSK1, or LEPR deficiency
Dr. Clément, professor of nutrition at Pitié-Salpêtrière Hospital and Sorbonne Université in Paris presented a poster entitled, “Timing of Onset of Adverse Events with Setmelanotide, an MC4R Agonist, in Patients with Severe Obesity Due to LEPR or POMC Deficiency.”

This presentation provided data from analyses of three studies that evaluated setmelanotide in obesity due to POMC, PCSK1 or LEPR deficiency. The analysis included 35 patients (15 POMC, 2 PCSK1, 18 LEPR) across three trials. Consistent with prior clinical experience, AEs of special interest included hyperpigmentation disorders, disturbances in sexual arousal, nausea, vomiting, and injection site reactions. The onset of AEs of special interest was generally highest during the first month of treatment, with fewer events occurring during subsequent months. Apart from hyperpigmentation, all AEs resolved quickly after onset.

The poster presentations will be available for on-demand viewing on the ENDO 2021 website, https://www.endocrine.org/endo2021, beginning at 11 a.m. on Saturday, March 20. The posters and slides from the oral presentation will be made available on Rhythm’s website, https://www.rhythmtx.com/publications/, following the presentations at ENDO 2021.

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. The Company's precision medicine, IMCIVREE™ (setmelanotide), has been approved by the 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. IMCIVREE is the first-ever FDA approved therapy for these rare genetic diseases of obesity. Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity. The Company 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. For healthcare professionals, visit www.UNcommonObesity.com for more information. For patients and caregivers, visit www.LEADforRareObesity.com for more information. The company is based in Boston, MA.

IMCIVREE™ (setmelanotide) Indication
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).

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 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, and our business strategy and plans, 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, 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, 2020 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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