Rhythm Pharmaceuticals Presents Initial Data from Long-term Extension Trial Evaluating Setmelanotide in Rare Genetic Diseases of Obesity at ENDO 2022

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-- Continued reductions in BMI observed following one year of setmelanotide treatment in patients with SH2B1 or SRC1 deficiency obesities or POMC or LEPR insufficiency obesities (heterozygous) --

-- Long-term reductions in BMI support probability of success in ongoing pivotal Phase 3 EMANATE clinical trial --

BOSTON, June 13, 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 new data from the Company's long-term extension (LTE) trial, which show continued body mass index (BMI) and weight reductions in patients with SH2B1 or SRC1 deficiency obesity, or with POMC or LEPR insufficiency obesity (heterozygous). Rhythm and its collaborators delivered these data in one oral presentation and two posters at the Endocrine Society Annual Meeting & Expo (ENDO), being held June 11-14, 2022 in Atlanta.

"We are excited to share initial data from the LTE trial evaluating setmelanotide in patients with obesity due to SRC1 or SH2B1 deficiency, or POMC or LEPR insufficiency caused by heterozygous variants in the *POMC, PCSK1, or LEPR* genes," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "Consistent with our experience in other rare genetic diseases of obesity, these data demonstrate that ongoing treatment with setmelanotide delivers continued improvement in weight-related measures. Importantly, these data also reinforce our confidence in the design of the placebo-controlled Phase 3 EMANATE clinical trial, for which we are enrolling patients with each of these genetic variants, in hopes of focusing on those patient populations with impaired signaling in the melanocortin-4 receptor (MC4R) pathway who have highest probability of responding to our precision therapy, setmelanotide. We continue to enroll patients in EMANATE, which, if successful, will support our ability to make setmelanotide available to many more people living with rare genetic diseases of obesity."

SH2B1 Deficiency Obesity
A total of 19 patients with obesity due to SH2B1 deficiency caused by a variant in the *SH2B1* gene or 16p11.2 deletion encompassing the *SH2B1* gene (SH2B1 deficiency obesity) who were treated with setmelanotide in the Phase 2 Basket Trial continued into the LTE trial. These data were presented in a poster, "Body Mass Index and Weight Reduction in Patients with SH2B1 Deficiency Obesity After 1 Year of Setmelanotide," by Sadaf Farooqi, M.D., Ph.D, the Wellcome-MRC Institute of Metabolic Science at the University of Cambridge. Highlights include:

- Nineteen (19) patients with SH2B1 deficiency entered the LTE trial, with 19, 15, and 14 of those patients having received at least 6, 9, and 12 months of treatment as of Oct. 29, 2021, respectively.
- Across all patients, including those who did not achieve 5% weight loss in the Phase 2 Basket Trial but chose to enter the LTE, the mean (SD) percent change in BMI was −3.4% (8.1%; n=19), −5.9% (10.0%; n=15), and −9.7% (8.0%; n=14) at 6, 9, and 12 months on therapy, respectively;
- Responders were defined as patients who achieved ≥5% weight loss at Month 3:
    - Across responders, the mean percent change in BMI was -8.8% (n=8), -9.1% (n=9) and -12.3% (n=9) at 6, 9 and 12 months on therapy, respectively; and
    - Across non-responders, the mean percent change in BMI was 0.6% (n=11), -1.1% (n=6) and -4.9% (n=5) at 6, 9 and 12 months on therapy, respectively.
- Seventeen (17) patients were continuing to receive setmelanotide therapy in the LTE trial as of the data cut off, while two patients had discontinued voluntarily. No patients discontinued due to adverse events.

SRC1 Deficiency Obesity
A total of 17 patients with obesity due to SRC1 deficiency caused by a variant in the *NCOA1* gene who were treated with setmelanotide in Rhythm's exploratory Phase 2 Basket Trial continued into the LTE trial. These data were presented in a poster, "Body Mass Index and Weight Reductions in Patients with SRC1 Deficiency Obesity After 1 Year of Setmelanotide," by Jesús Argente, M.D., Ph.D., Universidad Autónoma de Madrid in Spain. A deficiency in the SRC1 protein may be due to a variant on the *NCOA1* gene. Highlights include:

- Seventeen (17) patients with SRC1 deficiency entered the LTE trial, with 18, 13 and 10 of those patients having received at least 6, 9, and 12 months of treatment as of Oct. 29, 2021, respectively.
- Across all patients, including those who did not achieve 5% weight loss in the Phase 2 Basket Trial but chose to enter the LTE, the mean (SD) percent change in BMI was −5.7% (5.6%; n=16), −7.8% (5.8%; n=11), and −10.1% (9.4%; n=8) at 6,

9, and 12 months on therapy, respectively;
- Responders were defined as patients who achieved ≥5% weight loss at Month 3:
  - Across responders, the mean percent change in BMI was -10.1% (n=7), -10.5% (n=6) and -14.3% (n=3) at 6, 9 and 12 months on therapy, respectively; and
  - Across non-responders, the mean percent change in BMI was -2.3% (n=9), -4.7% (n=5) and -7.5% (n=5) at 6, 9 and 12 months on therapy, respectively.
- Fifteen (15) of 17 patients with SRC1 deficiency were continuing to receive setmelanotide therapy in the LTE trial as of the data cut off, while two patients had discontinued voluntarily. No patients discontinued due to adverse events.

POMC or LEPR insufficiency obesity (heterozygous)
A total of 17 patients with obesity caused by heterozygous variants in the *POMC, PCSK1* or *LEPR* genes who were treated with setmelanotide in the Phase 2 Basket Trial continued into the LTE trial. These data were delivered orally by Brieana Buckley, PharmD, M.S., Vice President of Medical Affairs at Rhythm, in a presentation entitled, "Body Mass Index and Weight Reductions in Patients with Obesity Due to Heterozygous Variants in *POMC*, *PCSK1*, or *LEPR* After 1 Year of Setmelanotide." Highlights include:

- Seventeen (17) patients with POMC or LEPR insufficiency obesity reached 12 months on therapy as of Oct. 29, 2021.
- Across all patients, the mean (SD) percent change in BMI was −7.9% (7.2%; n=16), -9.0% (8.6%; n=17), and −8.7% (8.2%; n=17) at 6, 9, and 12 months on therapy, respectively; and
- Patients 18 years old and older (n=15) achieved a mean (SD) percent change in body weight of −8.9% (6.8%; n=15), −11.7% (7.3%; n=14), and −10.2% (7.9%; n=15) at 6, 9, and 12 months on therapy, respectively; and
- 53.3% of patients 18 years old and older achieved greater than 10% weight loss at 12 months on therapy.
- Seventeen (17) patients with POMC or LEPR insufficiency obesity reached 12 months on therapy as of Oct. 29, 2021. Fifteen of those patients had enrolled in the LTE, five of those patients had discontinued voluntarily, and two patients who reached 12 months on therapy in the Basket Trial did not opt into the LTE. No patients discontinued due to adverse events.

Consistent with prior clinical observations, setmelanotide was generally well tolerated in the LTE trial across all indications and no new safety signals were observed.

Phase 3 EMANATE Trial Design
Dr. Farooqi also presented a poster entitled, "Setmelanotide in Patients With Obesity Due to Heterozygous Variants in *POMC, LEPR, NCOA1, or SH2B1* Genes: Design of EMANATE—a Placebo-Controlled Phase 3 Trial." As described in the poster, the EMANATE trial is comprised of four independent sub-studies evaluating setmelanotide in patients with: POMC insufficiency obesity, LEPR insufficiency obesity, SRC1 deficiency obesity and SH2B1 deficiency obesity. Rhythm plans to enroll approximately 400 patients with hyperphagia and obesity that began in early childhood in this trial. In each of the four sub-studies, patients will be randomized one-to-one to daily setmelanotide or placebo. The primary efficacy endpoint in each sub-study is the mean change from baseline to 52 weeks in body weight, assessed as percent change in BMI in response to setmelanotide compared to placebo. The first patient was enrolled in April 2022 and Rhythm anticipates 12-18 months to enroll the trial.

All Rhythm's presentations from ENDO 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2022 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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