Rhythm Pharmaceuticals Presents New Data from Phase 2 and 3 Trials Evaluating Setmelanotide in Multiple Rare Genetic Diseases of Obesity at the 59th Annual ESPE Meeting

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-- New subgroup analysis of Phase 3 data show setmelanotide achieved statistically significant weight loss and hunger reduction compared with placebo at 14 weeks in patients with Bardet-Biedl syndrome --
-- Efficacy results from complete topline analyses of Rhythm's Phase 2 Basket Study show weight loss and hunger reduction at three months on therapy in patients with SRC1 or SH2B1 deficiency --
-- Data from Phase 2 Basket Study also show clear separation between responders and non-responders in change in weight for adults and in BMI-Z scores for children and adolescents --

BOSTON, Sept. 22, 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 new data and analyses from phase 2 and 3 trials evaluating setmelanotide at the 59th Annual European Society for Paediatric Endocrinology (ESPE) Meeting, which is being held virtually this week.

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

- a new subgroup analysis of data from the 52-week, Phase 3 trial evaluating setmelanotide in Bardet-Biedl syndrome (BBS) that showed setmelanotide achieved statistically significant weight loss and hunger reduction compared to minimal effect observed with placebo during a 14-week, double-blind treatment period;
- complete topline analyses from the exploratory Phase 2 Basket Trial that showed setmelanotide achieved clinically meaningful weight loss or BMI-Z reduction in 30% (9 of 30) of study participants with obesity due to variants of the SRC1 gene; and
- complete topline analyses from the exploratory Phase 2 Basket Trial that showed setmelanotide achieved clinically meaningful weight loss or BMI-Z reduction in 43% (15 of 35) of study participants with obesity due to variants of the SH2B1 gene, including 16p11.2 chromosomal deletions.

"We know from decades of study that reduced activation of the central melanocortin-4 receptor (MC4R) pathway can lead to early-onset, severe obesity and a pathological hunger known as hyperphagia, which characterize rare genetic diseases of obesity," said Dr. Jesús Argente, who is an author on all three oral presentations and Professor in the Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid in Spain. "In these trials, treatment with setmelanotide, an MC4R agonist, provided patients across three distinct diseases – BBS, as well as obesity due to SRC1 or SH2B1 deficiency – with clinically meaningful reductions in weight loss and hunger. Together, these data support the potential for further development of setmelanotide for patients with rare genetic diseases of obesity driven by a range of variants in the MC4R pathway."

"In addition to presenting data from our Phase 2 and 3 trials of setmelanotide, we also presented posters at ESPE describing the gene selection process and the design of our Phase 2 DAYBREAK trial," said Linda Shapiro, M.D., Ph.D., Chief Medical Officer of Rhythm. "We are excited to share these presentations, which provide further rationale for our planned clinical development strategy. Collectively, these presentations depict setmelanotide's potential to deliver meaningful benefit – even without change in exercise or diet -- to people with obesity and variants in the SRC1 or SH2B1 gene, both of which are included in our Phase 3 EMANATE trial, and they support our decision to enroll people with obesity and variants in at least one of 31 other genes, all of which have 'strong' or 'very strong' MC4R pathway relevance, in our Phase 2 DAYBREAK trial. We look forward to initiating both EMANATE and DAYBREAK in the fourth quarter, which will evaluate setmelanotide on top of standard of care dietary and physical activity guidance, as we work to broaden setmelanotide's reach to many more patients with rare genetic diseases of obesity caused by variants in the MC4R pathway."

New Subgroup Analysis of Data from Phase 3 Trial in BBS
In a presentation entitled, "Phase 3 Trial of Setmelanotide in Participants with Bardet-Biedl Syndrome: Placebo-Controlled Results," Dr. Argente presented data from a 14-week double-blind treatment period, which preceded an open-label period that totaled 52 weeks on therapy. Highlights of the data include:

- Patients 12 years old or older treated with setmelanotide (n=14) compared to placebo (n=15) at 14 weeks demonstrated an average:
    - Greater weight loss of 3.8 kg, or 3%, of their baseline body weight ($p<0.05$);

    - Greater reduction in 'most hunger score' of 20.4% from baseline ($p<0.05$).
- All patients, including those younger than 12 years, treated with setmelanotide (n=16) achieved an average BMI reduction from baseline of 1.5 kg/m^2, or 3.8%, greater than patients treated with placebo (n=16) ($p<0.05$).

In December 2020, Rhythm announced that its Phase 3 trial evaluating setmelanotide in patients with BBS and Alström syndrome met its primary endpoint and all key secondary endpoints, with statistically significant and clinically meaningful reductions in weight and hunger at 52 weeks on therapy. All primary endpoint responders were patients with BBS; no patients with Alström syndrome met the primary endpoint.

Rhythm recently submitted a supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) and remains on track to submit a type II amendment to the European Medicines Agency (EMA) in the fourth quarter of 2021 for both BBS and Alström syndrome.

Complete Topline Analyses from Phase 2 Exploratory Basket Trial SRC1 and SH2B1 Cohorts
Rhythm also presented complete topline data from two genetic cohorts in its exploratory Phase 2 Basket Trial. These proof-of-concept data support the Company's pivotal EMANATE Phase 3 trial, a randomized, double-blind, placebo-controlled study with five independent sub-studies evaluating setmelanotide in patients with five distinct rare genetic diseases of obesity, including patients whose obesity is linked to certain variants of the SRC1 or SH2B1 genes. Based on genetic sequencing data and setmelanotide response rates achieved in the Basket Trial, Rhythm estimates that the five genetic indications being studied in the EMANATE trial represent a potential addressable patient population of approximately 100,000-200,000 people in the United States.

Phase 2 Data in Obesity Due to SRC1 Deficiency
Dr. Sadaf Farooqi of Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK, presented, "A Phase 2 Trial of the Melanocortin-4 Receptor Agonist Setmelanotide in Obesity Due to SRC1 Insufficiency: Body Weight, Body Mass Index Z Score, and Safety Results." A total of 30 patients with obesity and deficiency in the SRC1 gene were enrolled in the full analysis set of this study. The SRC1 gene is a key transcription modulator of *POMC,* certain variants of which are associated with early-onset, severe obesity. These patients had a mean BMI of 45.4 kg/m^2 or BMI-Z of 3.0 at baseline. BMI-Z, or BMI standard deviation score, represents the number of standard deviations from the median BMI for a child's age and sex. Highlights of the data include:

- Nine of 30 (30%) of patients achieved a clinically meaningful response to setmelanotide at three months, as defined by weight loss of 5% or greater from baseline, or for patients under 18 years old, a reduction of at least 0.15 in BMI-Z score:
    - In adult patients 18 years or older, six of 20 (30%) achieved 5% or greater weight loss at three months;
    - In patients younger than 18 years, three of 10 (30%) achieved a BMI-Z reduction of 0.15% or more at three months.
- Across all enrolled patients, the mean overall weight loss from baseline to three months among patients 18 years and older (n=20) was -4.0% (SD: 3.3%), and the mean overall BMI-Z score reduction from baseline to three months among patients younger than 18 years (n=10) was -0.21 (SD: 0.23).

In addition, the data show a clear separation between patients who responded to setmelanotide treatment at three months and those who did not:

- The mean body weight reduction for adult patients who responded (n=6) was 7.9% (90% CI, −9.7 to −6.0), as compared to 2.3% (90% CI, −3.2 to −1.4) for adult patients who did not respond (n=14);
- The mean BMI-Z reduction for patients younger than 18 years who responded (n=3) was 0.48 (90% CI, −0.95 to −0.01), as compared to 0.09 (90% CI, −0.11 to −0.07) for those who did not respond (n=7).

Phase 2 Data in Obesity Due to SH2B1 Deficiency
Cecilia Scimia, M.D., Ph.D., Medical Director at Rhythm, presented, "Efficacy and Safety Results of a Phase 2 Trial of Setmelanotide in Obesity Due to SH2B1 Variants and 16p11.2 Deletion Syndrome." A total of 35 patients with obesity and 16p11.2 deletions that include the SH2B1gene or deficiency in the SH2B1 gene, which is a promotor of leptin signaling in the MC4R pathway and can be associated with early-onset, severe obesity, were enrolled in the full analysis set of this study. These patients had a mean BMI of 47.2 kg/m^2 or BMI-Z of 3.6 at baseline. Highlights of the data include:

- Fifteen of 35 (42.9%) of patients achieved a clinically meaningful response to setmelanotide at three months, as defined by weight loss of 5% or greater from baseline, or for patients under 18 years old, a reduction of at least 0.15 in BMI-Z score:
    - In patients 18 or older, eight of 22 (36.4%) achieved 5% or greater weight loss at three months;
    - In patients younger than 18 years, seven of 13 (53.8%) achieved a BMI-Z reduction of 0.15% or more at three months.
- Across all enrolled patients, the mean overall weight loss from baseline to three months among patients 18 years and older (n=22) was -3.1% (SD: 3.9%), and the mean overall BMI-Z score reduction from baseline to three months among patients younger than 18 years (n=13) was -0.15 (SD: 0.13).

In addition, the data show a clear separation between patients who responded to setmelanotide treatment at three months and those who did not:

- The mean body weight reduction for adult patients who responded (n=8) was 7.2% (90% CI, −8.6 to −5.8), as compared to

0.8% (90% CI, −1.9 to 0.3) for adult patients who did not respond (n=14);
- The mean BMI-Z reduction for patients younger than 18 years who responded (n=7) was 0.25 (90% CI, −0.29 to −0.21), as compared to 0.03 (90% CI, −0.08 to 0.02) patients younger than 18 years who did not respond (n=7).

As previously reported, setmelanotide was generally well tolerated, with a consistent safety profile across these trials.

Additional Poster Presentations
Four additional abstracts were presented as posters:

Bhavik Shah, Ph.D., Senior Director Translational Research and Nonclinical Development, Rhythm Pharmaceuticals, presented, "An Evidence-based Framework to Evaluate Melanocortin-4 Receptor (MC4R) Pathway Relevance for Obesity-associated Genes." In this poster, Dr. Shah outlined Rhythm's evidence-based framework for gene selection criteria, which was used to identify MC4R pathway-relevant genes for inclusion in the Phase 2 DAYBREAK trial. The DAYBREAK trial is designed to evaluate setmelanotide in patients with specific variants in 31 genes classified under this framework as having "strong" or "very strong" relevance to the MC4R pathway.

Cecilia Scimia, M.D., Ph.D., Medical Director, Rhythm Pharmaceuticals, presented additional detail on the design of Rhythm's Phase 2 DAYBREAK trial in a separate poster, "Design of a Phase 2, Double-Blind, Placebo-Controlled Trial of Setmelanotide in Patients with Genetic Variants in the Melanocortin-4 Receptor Pathway."

Ida Moeller, ScD, ScM, MMSc, Director of Biomedical Informatics, Rhythm Pharmaceuticals, presented "Frequency of MC4R Pathway Variants in a Large US Cohort of Pediatric and Adult Patients with Severe Obesity." In this poster, Dr. Moeller reviewed updated data from individuals sequenced as part of Rhythm's Uncovering Rare Obesity ® (URO) genetic testing program. As of May 2021, Rhythm had sequenced genetic samples from 7,826 individuals in the United States with severe obesity, of which approximately 25% were found to be carrying a variant in one of 11 select MC4R pathway related genes. In July, Rhythm launched an updated URO genetic test with an expanded gene panel.

Jennifer Miller, M.D., Division of Pediatric Endocrinology, University of Florida, presented, "Efficacy and Safety of Setmelanotide in Individuals with Obesity Due to POMC or LEPR Deficiency: Phase 3 Results from Pivotal and Supplemental Cohorts." Highlights from this presentation include:

- A total of 85.7% of patients in the POMC trial (12/14; p<0.0001) and 53.3% of patients in the LEPR trial (8/15; p<0.0001) achieved ≥10% weight loss from baseline at 52 weeks;
- The mean percent change in body weight from baseline to 52 weeks was −25.8% (SD: 9.7%; p<0.0001) and −12.3% (SD: 7.5%; p<0.0001) in the POMC and LEPR trials, respectively.

All Rhythm's presentations from ESPE 2021 will be available following the meeting 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. The Company'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 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. The company is based 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 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, 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 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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