Rhythm Pharmaceuticals Announces Positive Topline Results from Pivotal Phase 3 Clinical Trial Evaluating Setmelanotide in Bardet-Biedl and Alström Syndromes

December 22, 2020

-- Study met primary endpoint and all key secondary endpoints with statistically significant and clinically meaningful reductions in weight and hunger --

-- All primary endpoint responders were patients with BBS --

-- Plan to submit sNDA to FDA for BBS in the second half of 2021 --

-- Company to host conference call today at 8 a.m. ET --

BOSTON, Dec. 22, 2020 (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 positive topline results from a pivotal Phase 3 clinical trial evaluating setmelanotide, the company's melanocortin-4 receptor (MC4R) agonist, for the treatment of insatiable hunger and severe obesity in individuals with Bardet-Biedl syndrome (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. All primary endpoint responders were patients with BBS. There were three evaluable patients with Alström syndrome and none of them met the primary endpoint.

"These Phase 3 results add to our growing understanding of setmelanotide's potential to treat people living with rare genetic diseases of obesity," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "We are pleased with the robust response observed in BBS patients, which supports our goal of delivering a precision medicine to this well-characterized patient population who suffer from insatiable hunger and severe, early-onset obesity. Although we are disappointed that none of the three evaluable Alström patients met the primary endpoint, we are encouraged by trends in hunger and weight reduction in some patients and look forward to evaluating the full data as we finalize our path forward in this indication."

Rhythm enrolled 32 individuals with BBS and six individuals with Alström syndrome in the pivotal cohort for this Phase 3 trial. The primary analysis was conducted on 31 evaluable participants (28 with BBS and three with Alström syndrome) 12 years old and older. Five study participants (three with BBS and two with Alström syndrome) were younger than 12 years old at enrollment.

The analysis of the primary endpoint shows:

- 11 of 31 or 34.5 percent[1] of participants achieved the primary endpoint of at least 10 percent reduction in body weight from baseline at approximately 52 weeks of therapy (p=0.0024);
    - 11 of 28 patients with BBS achieved 10 percent reduction in body weight;
    - 0 of 3 patients with Alström syndrome achieved 10 percent reduction in body weight.

The analysis of the key secondary endpoints shows:

- Mean reduction from baseline in body weight was -6.2 percent (p<0.0001);
- Mean reduction from baseline in most hunger rating was -30.8 percent (p<0.0001);
- 60.2 percent of participants achieved at least 25 percent reduction in most hunger scores from baseline at approximately 52 weeks of therapy (p<0.0001).

Consistent with prior clinical experience, setmelanotide was generally well tolerated:

- Treatment-emergent adverse events (TEAEs) included mild injection site reactions and nausea with infrequent vomiting;
- There were no serious adverse events (SAEs) related to treatment with setmelanotide;
- Eight patients discontinued from study drug treatment during the trial, five due to AEs (one on placebo at the time), and three for other reasons (one on placebo at the time).

"Despite conducting this trial during the COVID-19 pandemic, which has been linked to weight gain across many populations,

these data demonstrate that setmelanotide reduced weight and alleviated hunger in BBS patients. Overall, these results reinforce the potential value of the MC4R pathway as a therapeutic target for some rare genetic diseases of obesity and underscore our belief that obesity is a complex, multifactorial disease," said Murray Stewart, M.D., Chief Medical officer of Rhythm. "We are particularly pleased by these results given that nearly half of the evaluable patients were growing adolescents, who we would normally expect to gain weight. We look forward to completing further analyses on the full data, which will include BMI and BMI-Z scores, two measures that more accurately assess weight gain in adolescents and may further demonstrate the impact from treatment with our precision therapy."

Rhythm plans to complete regulatory submissions to both the U.S. Food and Drug Administration (FDA) and the European Medicines Association (EMA) for BBS in the second half of 2021. The company expects to finalize a path forward for Alström syndrome upon completing a full analysis of the final data from this trial.

About the Pivotal Phase 3 Trial in BBS and Alström Syndrome
The combined pivotal Phase 3 trial is a multinational, open-label, single-arm study consisting of 52 weeks of treatment with setmelanotide. Participants were blinded and randomized for the first 14 weeks of the trial to receive either placebo or setmelanotide therapy. Those participants who began the trial on setmelanotide continued therapy for a total of 52 weeks, while those on placebo went on to receive 52 weeks of setmelanotide therapy after completion of the 14-week placebo period.

Based on the statistical analysis plan, the primary analysis was completed for 28 of the 31 patients who reached or exceeded 52 weeks on setmelanotide therapy, as well as three patients who were randomized to the placebo group during the 14-week double-blind period, who have not yet reached 52 weeks on therapy. The Company expects to complete a subsequent analysis of the full data in the first quarter of 2021. Rhythm anticipates sharing the full data from this Phase 3 clinical trial in a forthcoming publication or in a presentation at an upcoming medical meeting.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8:00 a.m. ET today to discuss these clinical data. The conference call may be accessed by dialing (844) 498-0570 (domestic) and (409) 983-9726 (international) and referring to conference ID 3794695. A webcast of the conference call will be available in the Investors section of the Rhythm website at ir.rhythmtx.com. The archived webcast will be available on Rhythm's website approximately two hours after the conference call and will be available for 90 days following the call.

About Bardet-Biedl and Alström Syndromes
BBS and Alström syndrome are ultra-rare genetic diseases that affect multiple organ systems. Clinical features of BBS may include cognitive impairment, polydactyly, renal dysfunction, hypogonadism, and visual impairment. Clinical features of Alström syndrome may include progressive visual and auditory impairment, insulin resistance and Type 2 diabetes, hyperlipidemia, progressive kidney dysfunction, cardiomyopathy, and short stature in adulthood. Insatiable hunger, also known as hyperphagia, and severe obesity beginning early in life may be common in people living with either BBS or Alström syndrome. There is great variability in presentation and severity of these symptoms across individuals with BBS or Alström syndrome. In the United States, the Company estimates that BBS affects approximately 1,500 to 2,500 people and that Alström syndrome affects approximately 500 people. Currently, there are no approved therapies targeting the MC4 receptor pathway for reducing body weight and hunger in BBS or Alström syndrome.

About Setmelanotide
Setmelanotide is an MC4R agonist. The MC4 receptor is part of the key biological pathway that independently regulates hunger, caloric intake, and energy expenditure. Variants in genes may impair the function of the MC4R pathway, potentially leading to hyperphagia and early-onset, severe obesity. Rhythm is currently developing setmelanotide as a targeted therapy to potentially restore the function of an impaired MC4R pathway and, in so doing, potentially reduce hunger and weight in patients with rare genetic diseases of obesity. In November 2020, the FDA approved IMCIVREE™ (setmelanotide) 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 confirmed by genetic testing. The FDA has also granted Breakthrough Therapy designation to setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4R pathway, which includes BBS and Alström syndrome. The EMA has granted PRIority MEdicines (PRIME) designation for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency diseases of the MC4R pathway.

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 more than 30,000 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, including our expectations surrounding potential regulatory submissions and timing thereof, and our business strategy and plans. Statements using words 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 September 30, 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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[1] Response rate is based on imputation methodology accepted by FDA. All 11 responders were BBS patients; of the 11, two were initially randomized to placebo and had not reached 52 weeks of treatment at data cut.

Source: Rhythm Pharmaceuticals, Inc.