Rhythm Pharmaceuticals Announces Positive Data with Setmelanotide in Additional MC4R Pathway Deficiency-related Obesities

January 26, 2021

-- Clinical data from Phase 2 Basket Study including five cohorts totaling 65 patients demonstrated proof-of-concept in HET POMC, PCSK1 or LEPR deficiencies, SRC1 and SH2B1 deficiency obesities –

-- Phase 2 Basket Study responder rates and updated sequencing results suggest 100,000-200,000 potentially setmelanotide-responsive HET POMC, PCSK1 or LEPR deficiencies and SRC1 or SH2B1 deficiency obesity patients in U.S. --

-- New data from pivotal Phase 3 trial in Bardet-Biedl syndrome showed statistically significant and clinically meaningful improvements in pediatric BMI-Z scores --

-- Plan to initiate new pivotal MC4R Pathway Study to evaluate setmelanotide for treatment of HET obesity and SRC1 or SH2B1 deficiency obesities and new exploratory Basket Trial in patients with obesity defined by variants in one of 31 MC4R pathway-associated genes --

-- Virtual R&D event today; live webcast begins at 8 a.m. ET --

BOSTON, Jan. 26, 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 positive proof-of-concept data from multiple cohorts in its Phase 2 Basket Study evaluating setmelanotide in patients with severe obesity due to genetic variants in the melanocortin-4 receptor (MC4R) pathway, and provided an update on its genetic sequencing efforts. Rhythm will review these updates at its virtual Research & Development event, beginning today at 8 a.m. ET.

Rhythm provided a comprehensive update on its clinical development efforts with setmelanotide, including new interim data from its ongoing Phase 2 Basket Study and pivotal Phase 3 trial in Bardet-Biedl syndrome (BBS) and Alström syndrome. The Company also discussed plans to initiate a potentially registration-enabling Phase 3 trial evaluating setmelanotide in patients with MC4R pathway deficiencies due to a variant in one of the two alleles in the *POMC*, *PCSK1*, or *LEPR* genes (HET obesity), as well as the *SRC1* and *SH2B1* genes. Additionally, Rhythm provided an update on its sequencing efforts, now comprised of samples from approximately 37,500 individuals with severe obesity, and detailed an additional planned exploratory study to evaluate setmelanotide for the treatment of obesity due to a deficiency in one of 31 additional genes associated with the MC4R pathway.

Rhythm estimates, based on the response rates observed in its Phase 2 Basket Study, together with the updated sequencing results, that there are between 100,000 and 200,000 people with HET obesity or SRC1 or SH2B1 deficiency obesity in the U.S. who could potentially benefit from setmelanotide therapy.

“This is an exciting moment for Rhythm as we enter a new frontier in the treatment of rare genetic diseases of obesity,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “These new data show that setmelanotide led to meaningful weight loss in approximately 30 percent to greater than 50 percent of treated patients with genetic variants in the MC4R pathway across multiple genes. Across the setmelanotide development program we have been encouraged that patients who lost 5 percent or more weight in the first 12 to 16 weeks of therapy - our responder group - tended to go on to lose more weight over time. We believe these new data, coupled with our translational research and sequencing efforts, further validate our gene-selection strategy and support advancement into later-stage studies for certain genetic variants, as well as the expansion of our earlier-stage setmelanotide development program into as many as 31 additional MC4R pathway genes later this year. Moreover, the positive interim data in these new patient cohorts, while representing diseases which are individually rare, expand our estimates of the potential of setmelanotide to serve a far larger cumulative patient population than has been examined to date.”

Murray Stewart, M.D., Chief Medical Officer of Rhythm, added, “We have deepened our understanding of the impact of setmelanotide in specific populations, showing a statistically significant and clinically meaningful reduction in BMI-Z scores among BBS pediatric patients in our pivotal Phase 3 trial in BBS and Alström syndrome. BMI-Z scores correct for the fact a child or adolescent may be growing in height, and therefore would be expected to gain weight. These data increase our confidence in setmelanotide’s potential as a precision medicine for patients with a range of MC4R pathway variants and reinforce our commitment to working with urgency to maximize setmelanotide’s reach.”

Updated Interim Clinical Data from Phase 2 Basket Study

Rhythm today announced new proof-of-concept interim data from its ongoing Phase 2 Basket Study across individuals with one of three distinct rare genetic diseases of obesity: HET obesity due to a genetic variant in one of the two alleles of the *POMC, PCSK1* or *LEPR* gene (HETs); obesity due to SRC1 deficiency (SRC1); and obesity due to SH2B1 deficiency (SH2B1). Across five cohorts, 65 patients with severe obesity were eligible for analysis as of a cutoff date of Dec. 17, 2020.

The primary endpoint of the study is the percent of patients in each subgroup showing at least a 5 percent loss of body weight over three months.

HET Obesity (POMC, LEPR, PCSK1) highlights include:

- Overall, 12 of 35 patients (34.3 percent) achieved the primary endpoint. This full analysis includes six patients who withdrew early.
- Mean reduction from baseline in body weight across all 35 patients was -3.7 percent, which includes both clinical responders and non-responders;
- Among the 12 patients who achieved the primary endpoint (responder group), the mean reduction from baseline in body weight was -10.1 percent;
- Patients with HET obesity were stratified into three pre-specified cohorts by classification of their genetic variants according to American College of Medical Genetics (ACMG) guidelines:
    - Four of eight patients (50.0 percent) with a pathogenic or likely pathogenic variant achieved greater than 5 percent weight loss;
    - Four of eight patients (50.0 percent) with the N221D variant of the *PCSK1* gene achieved greater than 5 percent weight loss;
    - Four of 19 patients (21.1 percent) with a variant of unknown significance (VOUS) achieved greater than 5 percent weight loss.

Data from the SRC1 and SH2B1 cohorts were based on an interim analysis of patients who completed 12 weeks of therapy. This analysis did not include 15 patients who withdrew early due to COVID-related issues, adverse events or were lost to follow-up. Also not included were data from 12 patients who remain ongoing but have not yet reached 12 weeks of therapy.

Obesity due to SRC1 deficiency highlights include:

- Four of 13 patients (30.8 percent) achieved the primary endpoint;
- Mean reduction from baseline in body weight across all 13 patients was -3.7 percent, which included both clinical responders and non-responders;
- Among the four patients who achieved the primary endpoint (responder group) the mean reduction from baseline in body weight was -8.4 percent.

Obesity due to SH2B1 deficiency highlights include:

- Nine of 17 patients (52.9 percent) achieved greater than 5 percent weight loss over 12 weeks of therapy;
- Mean reduction from baseline in body weight across all 17 patients was -3.9 percent, which included clinical responders and non-responders;
- Among the nine patients who achieved the primary endpoint (responder group), the mean reduction from baseline in body weight was -7.1 percent.

Consistent with prior clinical experience, setmelanotide was generally well tolerated in each of these rare genetic diseases of obesity. The most common treatment-emergent adverse events (TEAEs) included mild injection site reactions, hyperpigmentation, and nausea and vomiting, which occurred early in the treatment course. There were no serious adverse events (SAEs) related to treatment with setmelanotide.

The Company is in discussions with the U.S. Food and Drug Administration (FDA) to define a potential path for setmelanotide towards registration for these indications. Pending the outcome of these discussions, Rhythm plans to initiate a pivotal Phase 3 trial evaluating setmelanotide in patients with HET obesity and SRC1 and SH2B1 deficiency obesities in the second half of 2021.

Setmelanotide Showed Statistically Significant and Clinically Meaningful Improvements in BMI-Z Scores in Pediatric Patients with BBS

In December 2020, Rhythm announced that the 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, with patients with BBS comprising all primary endpoint responders. No patients with Alström syndrome met the primary endpoint.

Today, Rhythm shared data from a predefined exploratory endpoint showing the impact of setmelanotide on BMI-Z scores for patients younger than 18 years old with BBS. The BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex. Setmelanotide was associated with statistically significant and clinically meaningful reductions in BMI-Z scores in patients with BBS:

- In 16 patients younger than 18 with BBS, the mean BMI-Z score was reduced from 3.74 at baseline to 2.98 for a reduction of -0.76, or -24.5 percent (p=0.0006).

Rhythm remains on track to complete regulatory submissions to both the FDA and European Medicines Agency (EMA) for BBS in the second half of 2021. The Company expects to determine next steps for Alström syndrome upon completing a full analysis of the final data from the Phase 3 trial.

Genetic Sequencing Data from Approximately 37,500 Obese Individuals Provides Updated U.S. Prevalence Estimates for HET Obesity, SRC1 and SH2B1 Deficiency Obesities

Rhythm, together with its collaborators, continues to expand its sequencing efforts in individuals living with early-onset, severe obesity. Since September 2019, Rhythm has increased its internal database of sequencing samples from 13,567 to approximately 37,500. The Company is using these data to support its research, patient finding and community building efforts in order to better understand rare genetic diseases of obesity.

Rhythm's genetic sequencing results demonstrated that approximately 10 to 15 percent of obese individuals sampled as of Sept. 30, 2020, showed a relevant MC4R pathway genotype in the *POMC*, *PCSK1*, *LEPR* HETS, and *SRC1* or *SH2B1* genes. The Company estimates, based on a combination of these sequencing yields, as well as clinical data on setmelanotide response rates among patients with variants in these genes, that there are 100,000 to 200,000 potentially setmelanotide-responsive patients in the United States with these rare genetic diseases of obesity.

Expansion of the Rhythm Basket Study into Additional 31 MC4R Pathway Genes

Rhythm also presented its proprietary gene curation and selection strategy specifically designed to evaluate a gene's relevance to the MC4R pathway with the goal of identifying genetic patient populations with the potential to benefit from setmelanotide therapy. Using this proprietary approach, Rhythm has identified an additional 31 MC4R pathway genes with strong or very strong pathway relevance, which it plans to evaluate in its expanded basket trial.

"We believe the new data presented today validate our proprietary approach to gene selection and efficient clinical development. Leveraging our extensive scientific expertise and years of internal research, we have developed a process that allows us to identify new genes that may be responsive to setmelanotide and to quickly advance them into our Basket Study for clinical evaluation," said Alastair Garfield, Ph.D., Vice President, Head of Translational Research of Rhythm Pharmaceuticals. "Based on our success across a range of genes with strong and very strong pathway relevance, we look forward to potentially expanding our clinical development program into patients with an additional 31 pathway genes later this year."

Pending discussions with the FDA, Rhythm plans to initiate a new exploratory MC4R Pathway Basket Trial in patients with 31 new genes in the second half of 2021.

Webcast Information:
The live webcast of today's event will be available under "Events & Presentations" in the Investors & Media section of the Company's website at http://www.rhythmtx.com. A replay of the webcast will be available on the Rhythm website for 30 days following the event.

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 timing and expansion of clinical trials, the number of U.S. patients with HET obesity or SRC1 or SH2B1 deficiency obesity who may be responsive to setmelanotide, validation of the Company's gene-selection strategy, efficient clinical development, advancement into later-stage studies and expansion of its earlier-stage development program, the expansion of the estimated number of patients who may be responsive to setmelanotide, regulatory plans, future development for the treatment of Alström syndrome, and identifying genetic patient populations that may potentially be treated with setmelanotide. 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 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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Source: Rhythm Pharmaceuticals, Inc.