Rhythm Pharmaceuticals Announces Updates on MC4R Pathway Programs at R&D Event

December 6, 2023

-- Phase 3 trial evaluating setmelanotide in pediatric patients ages 2-<6yo (N=12) over 52 weeks achieved primary endpoint --

-- Setmelanotide achieved 3.04 mean reduction in BMI-Z score and 18.4 percent mean reduction in BMI in patients ages 2-<6yo with obesity due to POMC/LEPR deficiency or BBS --

-- RM-718 showed potential to reduce body weight and hyperphagia with no off-target cardiovascular effects and no hyperpigmentation observed in pre-clinical studies; first in-human studies anticipated to begin in the first half of 2024 --

-- Responder rates of 25 to 56 percent demonstrated in six genetic cohorts of Phase 2 DAYBREAK trial of setmelanotide --

-- Company to host R&D webcast today at 8:00 a.m. ET--

BOSTON, Dec. 06, 2023 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases, today hosted an R&D event for investors and analysts, “Rhythm Update on MC4R Pathway Programs.”

During the event, the Company announced new topline data from its ongoing Phase 3, open-label pediatrics trial evaluating one year of setmelanotide therapy in patients between the ages of 2 and younger than 6 years with Bardet-Biedl syndrome (BBS) or proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency obesity and new preliminary data from the first stage of its exploratory Phase 2 DAYBREAK trial. Rhythm also presented pre-clinical data on its new drug candidate, RM-718, which is designed to be a more selective MC4R agonist with weekly administration, and its plans for Phase 1 clinical development.

The Company hosted Amy Wood, Executive Director and Co-Founder of the Raymond A. Wood Foundation, and Jennifer Miller, MD, Professor of Pediatric Endocrinology, University of Florida, who shared insights on hypothalamic obesity and the severe impact of the disease on patient quality of life. Rhythm continues to advance the development of setmelanotide in patients with hypothalamic obesity and remains on track to complete Phase 3 study enrollment by the end of 2023.

“Today, we are excited to showcase our commitment to understanding the MC4R pathway and developing the next generation of therapies,” said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. “Setmelanotide has demonstrated its potential to effect a clinically significant weight loss in children ages 2 to younger than 6 years old, potentially enabling us to treat patients younger in life when these diseases first present. With our DAYBREAK trial, we have shown potential for a meaningful, positive response to setmelanotide in several new gene cohorts.”

Setmelanotide demonstrated clinically meaningful reductions in BMI and BMI-Z score in patients aged 2 to <6 (N=12)
Today, Rhythm presented new data from its 52-week, Phase 3 pediatrics trial in patients between 2 and younger than 6 years old. The hyperphagia and severe obesity of rare genetically-caused MC4R pathway diseases can present early in life, and these data show potential efficacy in patients younger than 6. This trial is a multi-center, one-year, open-label trial in pediatric patients with obesity due to biallelic POMC, PCSK1 or LEPR deficiency or a clinical diagnosis of BBS with genetic confirmation. The primary efficacy endpoint is a responder analysis, based on the proportion of patients who experience a decrease from baseline in BMI-Z score of ≥0.2.

Highlights from the data include:

- 83.3% of all patients (10 of 12) achieved ≥ 0.2 reduction in BMI-Z score from baseline to week 52;
- 18.4 percent mean reduction from baseline in BMI at week 52 (N=12);
- 3.04 mean reduction from baseline in BMI-Z score at week 52 (N=12);
- 11 patients completed the trial, and all remain on therapy, as of Dec. 5, 2023; one patient discontinued and was lost to follow-up; and
- The safety profile is consistent with past trials evaluating setmelanotide.

Rhythm today also announced it has submitted 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 pediatric patients between 2 and younger than 6 years old with BBS or POMC, PCSK1 or LEPR deficiency in the European Union. The Company anticipates submitting a supplementary New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) in the first half of 2024 seeking a similar label expansion.

RM-718 demonstrated potential to reduce body weight and hyperphagia with a favorable safety profile and no hyperpigmentation in pre-clinical studies
Rhythm presented data from several pre-clinical studies showing that RM-718, a new, weekly, MC4R-specific agonist, demonstrated the potential to reduce body weight and hunger with a favorable safety profile. RM-718 is designed to be more highly targeted and MC1R sparing with the potential to not cause hyperpigmentation. The Company also showed data from pre-clinical studies demonstrating that RM-718 had no off-target cardiovascular effects in non-human primate studies.

Rhythm also announced today that it completed submission of a new investigational drug application for RM-718 to the FDA. The Company anticipates beginning Phase 1 in-human trials in the first half of 2024, including a multiple-ascending dose study in patients with hypothalamic obesity.

Data from Phase 2 DAYBREAK trial demonstrate potential efficacy of setmelanotide in multiple genetically-defined cohorts
Rhythm today also announced data from the open-label part of its exploratory Phase 2 DAYBREAK trial that demonstrate potential efficacy in patients in multiple genetically-defined cohorts. The Company presented data from the full analysis set for DAYBREAK, which includes 164 patients. A total of 112 patients completed the 16-week Stage 1 of the Phase 2 trial, with 52 patients who discontinued.

The primary endpoint of the trial is the proportion of patients by genotype who achieve a BMI reduction of ≥5% from baseline in response to setmelanotide at the end of Stage 1. The rates of response from Stage 1 of the trial were:

- 30% of patients (12 of 40) with variants in the *SEMA3* gene cohort;
- 35.6% of patients (16 of 45) with variants in the *PLXN*s gene cohort;
- 56.3% of patients (9 of 16) with variants in the *PHIP* gene cohort;
- 40% of patients (2 of 5) with variants in the *TBX3* gene cohort;
- 30% of patients (3 of 10) with variants in the *MAGEL2* gene cohort; and
- 25% of patients (5 of 20) with variants in the *SIM1* gene cohort.

For those who completed Stage 1, the rates of response of patients who achieved a BMI reduction of greater than 5% from a post-hoc analysis were:

- 44.4% of patients (12 of 27) with variants in the *PLXN*s gene cohort;
- 61.5% of patients (16 of 26) with variants in the *SEMA3* gene cohort than 5%; and
- 69.2% of patients (9 of 13) with variants in the *PHIP* gene cohort.

A total of 49 patients who completed Stage 1 with a response to setmelanotide were randomized into Stage 2 of the trial. Stage 2 is a 24-week, double-blind, placebo-controlled withdrawal study. These patients were stratified into genetically defined cohorts and randomized 2:1 to receive setmelanotide or placebo.

Rhythm anticipates announcing DAYBREAK Stage 2 data in the second half of 2024.

Conference Call Information
A live webcast of the R&D call will be available under "Events and Presentations" in the Investor Relations section of the Rhythm Pharmaceuticals website at https://ir.rhythmtx.com/. The archived webcast will be available on Rhythm Pharmaceuticals' website approximately two hours after the conference call and will be available for 30 days following the call.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) diseases. Rhythm's lead asset, IMCIVREE (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity caused by rare MC4R pathway diseases, is approved 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 monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). Both the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare MC4R pathway diseases, as well as a preclinical suite of small molecules for the treatment of congenital hyperinsulinism. Rhythm's headquarters is in Boston, MA.

Setmelanotide Indication
In the United States, setmelanotide is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) or BBS.

In the European Union, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) or genetically confirmed loss-of-function biallelic proopiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Limitations of Use
In the United States and Europe, Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide 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, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity.

WARNINGS AND PRECAUTIONS

Skin Monitoring: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing naevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and

during treatment with setmelanotide.

Heart rate and blood pressure monitoring: Heart rate and blood pressure should be monitored as part of standard clinical practice at each medical visit (at least every 6 months) for patients treated with setmelanotide.

Prolonged penile erection: Spontaneous penile erections have been reported in clinical trials with setmelanotide. Patients who have a penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment of priapism.

Depression: In clinical trials, depression has been reported in patients treated with setmelanotide. Patients with depression should be monitored at each medical visit during treatment with setmelanotide. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.

Pediatric Population: The prescribing physician should periodically assess response to setmelanotide therapy. In growing children, the impact of weight loss on growth and maturation should be evaluated. The prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Excipients: This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Patients who are pregnant or breastfeeding should be advised of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. This medicinal product should be used with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free.”

ADVERSE REACTIONS
The most frequent adverse reactions are hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache (26%).

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no data from the use of setmelanotide in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-fetal effects. As a precautionary measure, setmelanotide should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in fetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide treatment as there was no proof of teratogenicity in the nonclinical data. If a patient who is taking setmelanotide and still losing weight gets pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring for the recommended weight gain during pregnancy. The treating physician should carefully monitor weight during pregnancy in a patient taking setmelanotide.

Breast-feeding
It is unknown whether setmelanotide is excreted in human milk. A nonclinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from setmelanotide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility
No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337. See Summary of Product Characteristics' APPENDIX V for a list of European national reporting systems to communicate adverse reactions.

Please see the full Prescribing Information for additional Important Safety Information.

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, including for our Phase 2 DAYBREAK trial, anticipated development plan for RM-718 and regulatory submissions for our Phase 3 pediatrics program, our business strategy and plans, including regarding commercialization of setmelanotide in the United States and Europe, the application of genetic testing and related growth potential, and expectations surrounding the potential market opportunity for our product candidates.. Statements using word such as “expect”, “anticipate”, “believe”, “may”, “will”, "aim" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, risks relating to our liquidity and expenses, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks relating to product liability lawsuits, inability to maintain our collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, the impact of the COVID-19 pandemic and general economic conditions on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, failure to realize the anticipated benefits of our acquisition of Xinvento B.V. or significant integration difficulties related to the acquisition, and the other important factors discussed under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 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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