



## Rhythm Pharmaceuticals Announces Positive Interim Results from Phase 2 Clinical Trial Evaluating Setmelanotide in Hypothalamic Obesity

July 12, 2022

*--All evaluable patients (N=11) achieved BMI decrease of more than 5 percent at 16 weeks on setmelanotide therapy--*

*--17.2 percent mean reduction in BMI at 16 weeks--*

*--15.8 percent (15.9 kg or 35.1 lb) mean weight reduction achieved at 16 weeks--*

*--Mean change in hunger score of -2.7--*

*--Management to host conference call at 8:00 a.m. ET today--*

BOSTON, July 12, 2022 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a 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 announced positive interim results from a Phase 2 clinical trial evaluating setmelanotide, the Company's MC4R agonist, for the treatment of severe obesity and hyperphagia in people living with hypothalamic obesity. Based on the encouraging results observed, the Company intends to proceed to Phase 3 clinical development following consultation with regulatory agencies.

"Therapeutic options are very limited for patients with hypothalamic obesity, which is the result of damage to the medial hypothalamic region of the brain where MC4R pathway signaling is impaired due to certain tumors and their treatment. Surgical intervention, radiation treatment or even the growth and position of the tumor itself can leave patients with aggressive, rapid and debilitating weight gain," said M. Jennifer Abuzzahab, M.D., McNeely Pediatric Diabetes Center and Endocrine Clinic, Children's Minnesota and an investigator on the Phase 2 trial. "I believe these interim results for setmelanotide represent a major milestone for the hypothalamic obesity community. In this 16-week trial, patients receiving setmelanotide achieved a remarkable reduction in body weight, suggesting this precision therapy has the potential to transform the care of this rare, acquired obesity."

As of the data cutoff date of May 6, 2022, 11 patients were evaluable for assessment, including nine patients who completed 16 weeks of treatment and two patients who discontinued early due to treatment-related adverse events. Data highlights from an interim analysis of the full analysis set (N=11) include:

- -17.2 percent mean percentage change in BMI (range: -37.2 percent, -6.7 percent);
- -15.8 percent mean change (range: -34.9 percent, -6.7 percent) in body weight from baseline weight of 107.1 kg (range, 39.0 kg, 141.4 kg) or 236.1 lb;
- -15.9 kg (range, -28.2 kg, -6.7 kg) or -35.1 lb mean weight loss from baseline.

Data highlights from an interim analysis of completers (n=9) include:

- -19.5 mean percent change in BMI (range: -37.2 percent, -10 percent);
- -17.8 mean percent change (range: -34.9 percent, -10.7 percent) in body weight from baseline weight of 107.8 kg (range: 39.0 kg, 141.4 kg) or 236.1 lb;
- -17.8 kg (range: -28.2 kg, -9.5 kg) or -37.7 lb mean weight loss from baseline.

Setmelanotide also achieved a meaningful reduction in hunger scores. The mean change in hunger score for patients older than 12 years old who completed 16 weeks on therapy (n=7) was -2.7 on a scale of 1-10, with 10 being most hungry.

Consistent with prior clinical experience in other rare MC4R pathway diseases, setmelanotide was observed to be generally well tolerated. The most frequently reported treatment-emergent adverse events included nausea, vomiting, COVID-19, diarrhea, injection site reaction and abdominal pain.

"We are highly encouraged by these initial results, which reinforce the importance of the MC4R pathway in regulating hunger, caloric intake, energy expenditure and ultimately body weight, as well as the potential role of setmelanotide in the management of diseases where this pathway is impaired," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "We look forward to engaging with regulatory agencies to finalize our Phase 3 development plans in the months ahead, as we aim to expand our reach and make setmelanotide available to the approximately 5,000 to 10,000 people living with hypothalamic obesity in the United States."

### **About the Phase 2 Clinical Trial in Hypothalamic Obesity**

The Phase 2 clinical trial is a multi-center, open-label, proof-of-concept study that enrolled 18 patients with hypothalamic obesity who are between 6 and 28 years old. The trial consisted of 16 weeks of treatment with setmelanotide administered once daily by subcutaneous injection, including an initial period of dose titration. The primary endpoint is the percentage of patients who achieve more than 5 percent reduction in BMI from baseline after 16 weeks of treatment compared to a historic control of less than 5 percent in this population.

Of the 18 patients enrolled in this Phase 2 study, three discontinued due to adverse events, each of whom had achieved a reduction in BMI of more than 5 percent at the time they discontinued, and one patient was discontinued due to documented non-compliance to therapy. In total, 14 of 18 patients enrolled in this study remained on setmelanotide therapy as of July 11, 2022. Rhythm plans to present the full data from the 18 patients enrolled in this Phase 2 clinical trial at an upcoming medical meeting in the fall of 2022.

### **About Hypothalamic Obesity**

Hypothalamic obesity is a rare, acquired form of extreme obesity that occurs following damage to the hypothalamic region of the brain, which is responsible for controlling physiological functions such as hunger and weight regulation. It most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma or other rare brain tumors. Patients experience rapid weight gain, a reduction in energy expenditure an increase in hunger in the first six to 12 months following tumor resection, and ultimately develop severe obesity. In addition, people living with hypothalamic obesity may also experience delayed puberty and infertility, decreased physical activity, excessive daytime sleepiness, attention hyperactivity disorder, seizures and psychiatric conditions. Based on an analysis of incidence rates and prevalence reports of certain brain tumor types, as well as survival and obesity rates tied to these brain tumor types, Rhythm estimates there are approximately 5,000-10,000 patients living with hypothalamic obesity in the United States with approximately 500 new cases each year.

### **Conference Call Information**

Rhythm will host a live conference call and webcast at 8:00 a.m. ET today to discuss these data. Participants may register for the conference call [here](#). While not required, it is recommended that participants join the call ten minutes prior to the scheduled start.

A live webcast of the call will also be available under "Events and Presentations" in the Investor Relations section of the Company's website at <http://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 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) pathway diseases. Rhythm's precision medicine, IMCIVREE (setmelanotide), 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 POMC, PCSK1 or LEPR deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). The European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized IMCIVREE 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 living with these rare genetic diseases of obesity. The Company 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 adult and pediatric patients 6 years of age and older with BBS in the European Union. 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.

### **About Setmelanotide**

Setmelanotide is a melanocortin-4 receptor (MC4R) agonist. The MC4R is part of the key biological pathway that regulates hunger, caloric intake and energy expenditure. Variants in genes may impair the function of the MC4R pathway, potentially leading to decreased energy expenditure, hyperphagia and early-onset, severe obesity. Rhythm is developing setmelanotide as a targeted therapy to potentially restore the function of an impaired MC4R pathway and, in so doing, potentially increase energy expenditure, reduce hunger and weight in patients with rare genetic diseases of obesity.

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.

Rhythm's Type II variation application to the European Medicines Agency (EMA) for the treatment of obesity and control of hyperphagia in adult and pediatric patients 6 years of age and older with BBS is under review. The Company is continuing to advance the most comprehensive clinical research program ever initiated in MC4R pathway diseases, including the pivotal Phase 3 EMANATE clinical trial evaluating setmelanotide in four independent sub-studies in patients with obesity due to POMC insufficiency caused by heterozygous variants in the *POMC* or *PCSK1* genes, LEPR insufficiency caused by heterozygous variants in the *LEPR* gene, SRC1 deficiency caused by a variant in the *NCOA1* gene, and SH2B1 deficiency caused by a variant in the *SH2B1* gene or 16p11.2 deletion encompassing the *SH2B1* gene. The Phase 2 DAYBREAK trial is evaluating setmelanotide

in patients with severe obesity and hyperphagia caused by rare variants associated with 10 prioritized MC4R-relevant genes. Rhythm has also initiated a Phase 3 pediatric trial to evaluate setmelanotide in children between the ages of 2 and younger than 6 years old and a Phase 3 trial evaluating a weekly formulation of setmelanotide in patients actively receiving daily setmelanotide treatment.

### **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 monogenic or syndromic obesity due to:

- Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (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)
- Bardet-Biedl syndrome (BBS)

### **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, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity

### **WARNINGS AND PRECAUTIONS**

**Disturbance in Sexual Arousal:** Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

**Depression and Suicidal Ideation:** Depression and suicidal ideation have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

**Skin Pigmentation and Darkening of Pre-existing Nevi:** Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new 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. Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

### **ADVERSE REACTIONS**

- The most common adverse reactions (incidence  $\geq 20\%$ ) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

### **USE IN SPECIFIC POPULATIONS**

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at 833-789-6337 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**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 with respect to the Phase 2 clinical trial evaluating setmelanotide in hypothalamic obesity and the Phase 3 development strategy, our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of IMCIVREE. 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, 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 that interim, “topline” and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data risks associated with data analysis and reporting, our ability to successfully commercialize setmelanotide, 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 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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